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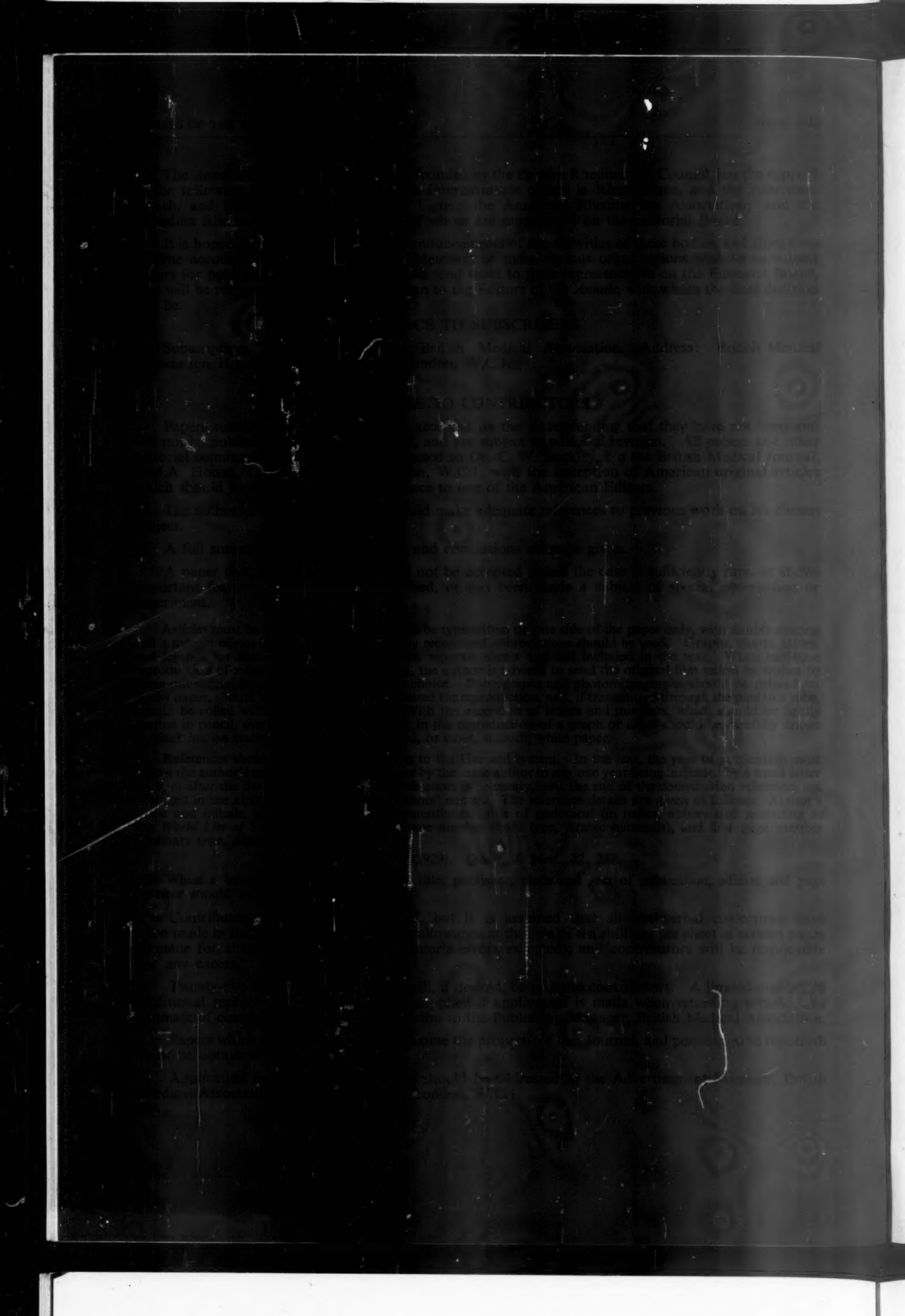

SHEEP CELL AGGLUTINATION TEST FOR RHEUMATOID ARTHRITIS

A CLINICO-PATHOLOGICAL STUDY

BY

J. BALL

Rheumatism Research Centre, University of Manchester

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A modification of the sheep cell agglutination test for rheumatoid arthritis devised by Rose (1949) has already been described (Ball, 1950); in a preliminary trial, this test was found to be positive in about half of the patients diagnosed clinically as suffering from rheumatoid arthritis. On the other hand, a positive result was but rarely found in patients diagnosed as suffering from other arthritic or rheumatic conditions with the possible exception of disseminated lupus erythematosus.

The clinicians co-operating in this investigation used the term rheumatoid arthritis for a variety of ill-defined polyarthritic syndromes as well as for typical cases of rheumatoid arthritis in which there is symmetrical involvement of the small joints of the hands and feet, subcutaneous nodules, vasospasm, lymphadenopathy, and constitution disturbances, and in which the diagnosis presents no difficulty. Furthermore, the diagnosis was made in most cases in the out-patient department. It was recognized at the outset that patients diagnosed as suffering from rheumatoid arthritis might not necessarily form a homogeneous clinical group.

The original studies have now been extended and a more detailed clinical analysis has been made of the positive and negative cases of rheumatoid arthritis, and of the false positive cases, to determine the relation of various clinical features to the result of the test.

Material and Methods

The findings here presented are based on an analysis of 1,943 cases studied between April, 1949, and December, 1950, included in which are the 895 cases previously reported. The source of clinical material was the same as that previously described, though in the latter part of the work control cases were obtained from various regional hospitals other than the Manchester Royal Infirmary. The results of the test and the clinical diagnoses were determined independently throughout the trial.

The technique (Ball, 1950) consisted of adsorbing inactivated human serum on normal sheep cells and then titrating this adsorbed serum with a suspension of sensitized sheep cells. If, after incubation for one hour at 37° C., agglutination occurred with a final serum dilution of 1 : 4 or more, the result was considered positive. The sensitivity of the sensitized sheep cell suspension (and hence the sensitivity of the test) was controlled by diluting anti-sheep rabbit serum until sheep cells sensitized by it were agglutinated " to titre " by an arbitrary standard human serum containing the agglutinating factor.

General Review of Results

Table 1A shows the results obtained at the first test of the 1,943 cases. It will be seen that 44·2 per cent. of the 642 cases of rheumatoid arthritis and 2·5 per

TABLE I
RESULTS IN 1,943 CASES, BASED ON (A) FIRST TEST, (B) MULTIPLE TESTS

Clinical Groups	Total	Positive (A)		Positive (B)	
		No.	% of Total	No.	% of Total
1. Rheumatoid Arthritis ..	642	284	44·2	304	47·4
2. Ankylosing Spondylitis ..	203	3	1·5	3	1·5
3. Osteo-Arthritis	249	8	3·2	8	3·2
4. Other Arthritides.. ..	289	15	5·2	19	6·6
5. Obscure Painful States ..	176	4	2·3	4	2·3
6. Rheumatic Fever and Subacute Rheumatism ..	47	0	0	0	0
7. Non-Arthritic Diseases ..	317	3	0·9	3	0·9
8. Normal	20	0	0	0	0
Total Groups 2-8	1,301	33	2·5	37	2·8

cent. of the control cases were positive. Most of the false positive reactions occurred with serum from patients suffering from some form of arthritic disease.

When patients were repeatedly tested at intervals, the result usually remained the same, but in some it changed from negative to positive or *vice versa*. Thus, of 106 cases of rheumatoid arthritis which were positive when first tested, 31 (29·2 per cent.) became negative at a later date; and of 117 cases of rheumatoid arthritis which were negative at the first test, 20 (17·1 per cent.) subsequently gave a positive result. However, only 4 (2·9 per cent.) out of 135 non-rheumatoid cases which were negative when first tested, later gave a positive result. Thus the additional positive reactions obtained by repeated tests occurred mainly among patients with rheumatoid arthritis. The total positive reactions, including these additional cases detected in multiple tests, are shown in Table IB.

Non-Rheumatoid Groups (Table I, 2-8).—Further consideration of the control groups is necessary, firstly to clarify the nature of the clinical material and secondly to assess the significance of the false positive reactions. The results quoted below are taken from sections of Table IB.

Group 2—Ankylosing Spondylitis.—The 203 cases are a continuous series of patients attending a special clinic for the study of ankylosing spondylitis. The test was negative in all but three cases. Most patients were tested before *x*-ray treatment, and in those re-tested after treatment the results were essentially the same. Among the last 117 cases were thirty in which active arthritis of joints distal to the hips and shoulders was a complicating feature. All of these thirty cases were negative.

Of the three false positive cases, two presented no unusual clinical features.

The remaining case was that of a female aged 52 who had suffered for some years from intermittent pain at different levels in the spine. About one year before examination she had developed stiffness and swelling of the fingers of both hands, and later the ankles, wrists, and knees became swollen and painful; at that time she was considered to be suffering from rheumatoid arthritis. On clinical examination only the sacro-iliac joints were abnormal and radiologically only the right sacro-iliac joint was involved, showing bony sclerosis and erosions. The clinical diagnosis was "atypical ankylosing spondylitis".

Group 3—Osteo-Arthritis.—Included in this group were many patients suffering from the generalized type of osteo-arthritis (Kellgren and Moore, 1952). Post-traumatic osteo-arthritis and osteo-arthritis associated with a slipped epiphysis or congenital dislocation were rare. All cases of osteo-arthritis complicating rheumatoid arthritis were excluded.

Of the 249 cases, eight were positive; and six of these eight were typical cases of osteo-arthritis. The other two false positive cases were atypical; the clinical findings in one of these are described below:

A female aged 58 years stated that at the age of 43 she had been laid up for 16 weeks with rheumatic fever. Thereafter she had suffered from fibrositis but no joint swelling had been noticed. Three months before examination she had wrenched her left knee, since when it had been painful and swollen. On examination there was marked peri-articular swelling of the left knee which was hot and tender. Clinically no other abnormality was found. *X*-ray examination showed that the joint space was reduced in both knees. The erythrocyte sedimentation rate (Westergren) was 96 mm. in the first hour.

Group 4—Other Arthritides.—The 289 cases were subdivided into 25 clinical types. Table II shows the distribution of the false positive reactions in this group.

TABLE II

CLINICAL TYPES AND RESULTS IN 289 CASES OF ARTHRITIC DISEASE (GROUP 4)

Type of Arthritic Disease	Total	No. Positive
1. Indeterminate arthritis	82	4
2. Disk lesions	51	0
3. Gout	18	1
4. "Infective" arthritis	17	2
5. Shoulder syndromes	13	0
6. Tuberculous arthritis	12	0
7. Disseminated lupus erythematosus	10	6
8. Atypical polyarthritis	9	2
9. Scleroderma	7	2
10. Acromegaly	6	0
11. Intermittent hydrarthrosis	6	0
12. Reiter's syndrome	5	0
13. Gonococcal arthritis	4	0
14. Osteochondrosis	4	0
15. Tuberculosis and rheumatism	4	0
16. Periarteritis nodosa	3	0
17. Allergic arthritis	3	1
18. Hypertrophic pulmonary osteo-arthropathy	3	0
19. Dermatomyositis	3	1
20. Syphilitic arthritis	3	0
21. Erythema nodosum	2	0
22. Haemarthrosis	1	0
23. Myelomatosis	1	0
24. Morquio's syndrome	1	0
25. Miscellaneous	21	0
Total	289	19

It will be seen that almost one-third of the positive cases were diagnosed as suffering from disseminated lupus erythematosus.

Type 1. This comprised 82 cases of indeterminate arthritis. Many were patients suffering from a destructive arthritis of one or two large joints. Isolated arthritis of the

cervical spine was also fairly common. Few presented with a generalized polyarthritis. The four patients in whom the test was positive presented no distinctive clinical features.

Type 3. This comprised eighteen cases of gout; in ten the diagnosis was beyond reasonable doubt, but in the remainder neither a raised blood uric acid nor gouty tophi were found. One of these unproven cases was positive in the test.

Type 4. The term " infective arthritis " is used here to describe patients with an asymmetrical or monarticular arthritis involving large rather than small joints and commonly associated with an obvious focus of infection, the removal of which is often followed by a remission of symptoms. Radiologically, subchondral bone sclerosis may be found in addition to the osteoporosis and bony erosions characteristic of rheumatoid arthritis.

Of the seventeen cases of " infective arthritis " two were positive, and one of these seems worthy of special note:

The patient was a male aged 37 who had suffered for the last three years from pain and stiffness in the fingers, knees, and feet. On examination no obvious focus of infection was noted. All the joints of the hands, feet, and wrists were swollen, tender, and limited in motion; the metacarpo-phalangeal joints of the feet showed dorsal subluxation. There was a subcutaneous nodule on one elbow. Radiologically, the wrists, knees, and hands showed subchondral bone sclerosis as well as generalized osteoporosis.

Type 8. This comprised nine cases of " atypical polyarthritis ", six being diagnosed as " multiple synovitis "—a condition characterized by multiple severely swollen but fairly mobile joints but no other clinical or radiological signs of the type usually associated with rheumatoid arthritis. Two of these cases were positive. There were also three cases of " diffuse capsulitis ", which was distinguished from rheumatoid arthritis in the same way as multiple synovitis, but joint stiffness and capsular thickening occurred rather than large effusions; all three were negative in the test.

The most striking finding in Group 4 was the occurrence of positive reactions in six of ten cases of disseminated lupus erythematosus. Positive results were also obtained in one of three cases of dermatomyositis, and one of seven cases of scleroderma, but the three cases of periarteritis nodosa were negative.

Group 5—Obscure Painful States.—Under this heading were included syndromes commonly known as " psychogenic rheumatism ", " muscular rheumatism ", " fibrositis ", and " neuritis ". In most cases there was no objective evidence of arthritis, but the erythrocyte sedimentation rate was 16 mm. or more in 54 (36 per cent.) of the 149 cases in which the test was performed, and it is conceivable that some of these patients were early cases of rheumatoid arthritis or of some other form of arthritic disease.

Of the 176 cases in this group, four were positive, and in these four cases the erythrocyte sedimentation rate was 64, 37, 44, and 4 mm. respectively. Unfortunately, a follow-up of these four cases has not been possible.

Group 6—Rheumatic Fever and Subacute Rheumatism.—There were 39 cases of acute rheumatism (rheumatic fever), five of subacute rheumatism, and three of chronic rheumatic fever in which persistent carditis was associated with a polyarthritis of the rheumatic fever type. Seventeen of the 39 cases of acute rheumatism were under 15 years of age, and eleven were between 30 and 45. Tests were made in both the active and convalescent stages of the disease. All the 47 cases in this group were negative.

Group 7—Non-Arthritic Diseases.—The 317 cases in this group included a wide variety of acute and chronic non-articular diseases. All were negative, with the exception of two cases of lobar pneumonia and one case of broncho-pneumonia, none of which presented any evidence of arthritic disease. Nine other cases of lobar pneumonia and two other cases of broncho-pneumonia were negative.

COMMENT.—The results in the control groups indicate the remarkable specificity of the test. Most of the false positive reactions occurred in patients suffering from some form of arthritic disease, and though some might have been included in the rheumatoid group, most showed no distinctive clinical features.

In respect of the agglutinating factor, it is obvious that ankylosing spondylitis is distinct from rheumatoid arthritis, and the test thus provides new evidence in support of the view that these two syndromes should be regarded as distinct disease processes (Hart and others, 1949). This distinction is true even of cases with active peripheral joint involvement. Heller and others (1949), whose technique is similar to mine, reported negative results in all of 22 cases of ankylosing spondylitis though patients with active peripheral joint involvement were not included.

Other syndromes that may resemble rheumatoid arthritis—such as acute and chronic rheumatic fever, " infective arthritis ", intermittent hydrarthrosis, and gout—gave almost uniformly negative results in the test. Similarly, osteo-arthritis, abnormalities of the intervertebral disks, and various bacterial arthritides were, with rare exceptions, also associated with a negative result. The striking exception to the rule of specificity occurred in cases of disseminated lupus erythematosus which were indistinguishable from rheumatoid arthritis in the agglutination test. Whether the same may be said of periarteritis nodosa, scleroderma, and dermatomyositis, which are often linked with disseminated lupus erythematosus on pathological grounds (Banks, 1941), remains to be seen, for as yet too few cases of these syndromes have been tested.

The occurrence of false positive reactions in three patients suffering from lobar or broncho-pneumonia remains unexplained. It seems unlikely to be due to streptococcal or pneumococcal infection *per se*, since many such cases have given negative results; moreover, according to Svartz and Schlossmann (1949), the serum of rabbits experimentally infected with either of these organisms does not enhance the specific agglutination of sheep erythrocytes.

The agglutination reaction appears to be independent both of the serum protein changes accompanying acute and chronic granulomatous processes and of a raised serum globulin level; this is evident from the negative results obtained in tuberculosis, sarcoidosis, osteomyelitis, and cases of myelomatosis known to have abnormally high serum globulin levels. Nor is there any evidence that the agglutinating factor is closely linked with adrenal cortical function, since negative results were obtained in cases of both Cushing's disease and Addison's disease.

Rheumatoid Arthritis Group (Table I, 1).—To facilitate the study of this group the analysis was based on the results obtained at the first examination of sera (Table I(A)). Of the total of 642 cases, 464 were females and 178 males. The incidence of cases according to the age at onset is shown in Table V. Judged

by these two criteria, the whole group is comparable with other series of cases of rheumatoid arthritis (Sclater, 1943; Lewis-Faning, 1950).

DISTRIBUTION OF CASES ACCORDING TO AGGLUTININ TITRE.—Of the total 642 cases, 284 were positive and the distribution of these positive cases according to their agglutinin titre is shown in Table III. The peak incidence for the whole group occurred at a titre of $\frac{1}{64}$, which corresponds to the fifth of the ten tubes over which the titre range was spread. The peak for males is at a higher titre than that for females, and the proportion of cases falling in the lower titre range ($\frac{1}{4}$ to $\frac{1}{16}$) is higher for females than for males.

TABLE III
DISTRIBUTION OF 284 CASES OF RHEUMATOID ARTHRITIS ACCORDING TO AGGLUTININ TITRE

Titre	Tube	Number			Per cent.		
		Male	Female	Total	Male	Female	Total
1/4	1	2	11	13	1·9	6·2	4·6
1/8	2	8	15	23	7·5	8·4	8·1
1/16	3	8	26	34	7·5	14·6	12·0
1/32	4	15	28	43	14·2	15·7	15·1
1/64	5	20	45	65	18·9	25·3	22·9
1/128	6	26	29	55	24·5	16·3	19·4
1/256	7	16	16	32	15·1	9·0	11·3
1/512	8	9	6	15	8·5	3·3	5·3
1/1024	9	2	1	3	1·9	0·6	1·0
1/2048	10	0	1	1	0	0 6	0·3
Total		106	178	284	100	100	100

RELATION OF TEST TO CLINICAL FEATURES.

(1) *Psoriatic Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis, and Rheumatoid Arthritis associated with Osteo-Arthritis.*

There were fourteen cases of rheumatoid arthritis associated with *psoriasis* (six males and eight females); all but one were negative.

None of the six *juvenile* cases aged 15 or under were positive, but of seven cases aged between 16 and 20, two gave positive results.

In nineteen patients (six males and thirteen females) *osteo-arthritis* was a complicating feature; ten of these (five males and five females) gave positive reactions.

(2) *Sex.*

Table IV shows that a higher proportion of males than females gave positive results in the test, the difference of proportions being 21·2 ± 4·3 per cent. Males are thus more likely to give a positive reaction than females.

TABLE IV
RELATION OF TEST TO SEX

Result	Total		Male		Female	
	No.	%	No.	%	No.	%
Positive	284	44·2	106	59·6	178	38·4
Negative	358	55·8	72	40·4	286	61·6
Total	642	100	178	100	464	100

Difference between proportions of Positive Cases in Males and Females = 21·2 ± 4·3.

(3) *Age at Onset.*

Table V shows the age at onset by sex and the incidence of positive cases in the various age groups. Comparing males and females, the proportion of cases in each age group is much the same. The peak incidence for males and females occurs in the group whose age at onset was 40- <50 years; incidentally, the fact that only 14 per cent. of males and 18·1 per cent. of females were aged under 30 at onset confirms the findings of Sclater (1943) that rheumatoid arthritis has in neither sex a predilection for the young adult.

In both males and females, the proportion of positive cases in each age group is about the same; a χ^2 test showed that the slight variations seen in the Table have almost certainly arisen by chance. A positive result therefore does not depend on the age at onset, though it should be mentioned that few patients aged under 20 at the time of the test were included.

TABLE V

RELATION OF TEST TO AGE AT ONSET

Age Group (years)	Total		Male		Female		Positive					
							Total		Male		Female	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
<20	35	5·5	7	3·9	28	6·0	13	37·1	3	42·9	10	35·7
20-<30	74	11·5	18	10·1	56	12·1	33	44·6	12	66·7	21	37·5
30-<40	151	23·5	42	23·6	109	23·5	66	43·7	25	59 5	41	37·6
40-<50	194	30·2	59	33·1	135	29·1	91	46·9	34	57·6	57	42·2
50-<60	116	18·1	29	16·3	87	18·7	50	43·1	19	65·5	31	35·6
60>	50	7·8	17	9·6	33	7·1	20	40·0	9	53·0	11	33·3
No Data ..	22	3·4	6	3·4	16	3·5	11	50·0	4	66·7	7	43·8
Total ..	642	100	178	100	464	100	284	44·2	106	59·6	178	38·4

Average age at onset: Males, 43 years; Females, 42 years.

(4) *Duration of Disease.*

If the cases are divided according to whether the duration of the disease was more or less than 3 years (Table VI), it is seen that, in both males and females, a significantly

TABLE VI

RELATION OF TEST TO DURATION OF DISEASE

Duration of Disease	Total		Male		Female		Positive					
							Total		Male		Female	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Up to 6 months	60	9·3	20	11·2	40	8·8	24	40·0	8	40·0	16	40·0
>6-12 months ..	64	10·0	21	11·8	43	9·3	17	26·5	9	42·9	8	18·6
>1-3 years ..	153	23·8	47	26·4	106	22·8	56	36·6	26	55·3	30	28·3
>3-6 years ..	116	18·1	30	16·9	86	18·5	58	50·0	20	66·7	38	44·2
>6-<10 years ..	63	9·8	16	9·0	47	10·1	31	49·2	11	68·7	20	42·5
10 and >10 years	154	24·0	34	19·1	120	25·9	85	55·2	28	82·4	57	47·0
No Data ..	32	5·0	10	5·6	22	4·6	13	40·6	4	40·0	9	40·9
Total ..	642	100	178	100	464	100	284	44·2	106	59·6	178	38·4
Up to 3 years..							35·0		48·9		28·6	
>3 years ..							52·3		73·7		45·5	
Difference ..							17·3 ± 4·0		24·8 ± 7·1		16·9 ± 4·5	

higher proportion of positive results occurred among patients with a clinical history of more than 3 years.

The further subdivisions shown in the Table are presented with caution, since the numbers in some of the sub-groups are small; but it should be mentioned that 40 per cent. of cases with a clinical history of up to 6 months were positive. Thus the test is capable of detecting early cases, and strongly positive reactions have in fact been found as early as 5 weeks after the onset of symptoms. The proportion of positive results increases with the duration of the disease; they were obtained in 41·5 per cent. of males with a history of up to one year as against 82·4 per cent. of males with a history of 10 years or more; in females, however, this trend is less clear and we find no such marked peak incidence. Table VI also shows that generally the disease had lasted longer in females than in males; the higher proportion of males giving a positive result cannot therefore be due to a longer duration of disease.

(5) *Nodule Formation.*

Subcutaneous nodules are one of the most characteristic clinical signs of rheumatoid arthritis; according to Bauer (1939) they occur in about 20 per cent. of cases. Table VII shows that subcutaneous nodules occurred in 15 per cent. in our sample, and more often in males than females.

TABLE VII

RELATION OF TEST TO NODULE FORMATION

Nodules	Total		Male		Female		Positive					
							Total		Male		Female	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Present	96	15·0	43	24·2	53	11·4	75	78·1	37	86·0	38	71·7
Absent	523	81·4	124	69·7	399	86·0	202	38·6	65	52·4	137	34·3
No Data ..	23	3·6	11	6·1	12	2·6	7	30·5	4	36·7	3	25·0
Total ..	642	100	178	100	464	100	284	44·2	106	59·6	178	38·4
Difference between Two Main Subgroups							39·5 ± 4·7		33·6 ± 6·9		37·4 ± 6·6	

Of the 96 cases with subcutaneous nodules, 78·1 per cent. were positive as compared with 38·6 per cent. of those without the lesion; there is thus a marked tendency for patients with subcutaneous nodules to give a positive result in the test. This association is present in both sexes.

(6) *X-ray Findings.*

The following radiological criteria were used in grouping the cases:

(*a*) No abnormality;
(*b*) Osteoporosis only;
(*c*) Advanced changes such as loss of joint space and bony erosions.

Since 34 per cent. of the total were not examined radiologically and the distribution of positive cases in this sub-group was uneven, it is difficult to assess the results. However, Table VIII shows that 21·1 per cent. of 57 cases in which *x* rays revealed no abnormality, and 39·4 per cent. of 94 cases showing only osteoporosis, were positive; it also indicates that in each sub-group the proportion of males and females is essentially the same.

(7) *Extent of Joint Involvement.*

The following criteria were used in grouping the cases:

(*a*) Only peripheral joints involved (wrists, ankles, hands, and feet being "peripheral", and all other joints "central").

TABLE VIII

RELATION OF TEST TO *X*-RAY FINDINGS

X-ray Findings	Total		Male		Female		Positive					
							Total		Male		Female	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Advanced Changes	273	42·5	77	43·3	196	42·3	149	54·6	60	77·9	89	45·4
Osteoporosis Only	94	14·6	20	11·2	74	15·9	37	39·4	8	40·0	29	39·2
Normal	57	8·9	18	10·1	39	8·4	12	21·1	7	38·9	5	12·8
No Data . .	218	34·0	63	35·4	155	33·4	86	39·5	31	49·2	55	35·5
Total . .	642	100	178	100	464	100	284	44·2	106	59·6	178	38·4

(*b*) Both peripheral and central joints involved.
(*c*) Only central joints involved.
(*d*) No objective evidence of joint disease.

The last subgroup contained ten patients (nine females and one male) who presented with a typical history of one or more rheumatoid episodes and other signs of the disease, but in whom no definite objective evidence of arthritis was found.

Table IX shows that positive results were found in 43·0 per cent. of 151 cases in which only peripheral joints were involved, but all but one of 25 cases in which only central joints were affected gave a negative result; thus the test clearly distinguishes this type of case from the average patient with rheumatoid arthritis.

TABLE IX

RELATION OF TEST TO EXTENT OF JOINT INVOLVEMENT

Joints Involved	Total		Male		Female		Positive					
							Total		Male		Female	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Peripheral and Central	427	66·5	115	64·6	312	67·3	205	48·0	74	64·3	131	42·0
Peripheral Only	151	23·5	43	24·2	108	23·3	65	43·0	24	55·8	41	38·0
Central Only . .	25	3·9	7	3·9	18	3·9	1	4·0	1	14·3	0	0
None	10	1·6	1	0·6	9	1·9	0	0	0	0	0	0
No Data . .	29	4·5	12	6·7	17	3·6	13	44·8	7	58·4	6	35·3
Total . .	642	100	178	100	464	100	284	44·2	106	59·6	178	38·4

In the whole group there is little difference in the proportion of positive results in patients with involvement of both peripheral and central joints and in patients with only peripheral joints involved. The distribution of cases according to the extent of joint involvement is closely similar in males and females.

(8) *Activity of Disease.*

The activity of rheumatoid arthritis is difficult to grade accurately, especially when, as in this study, the assessment is made in retrospect; the cases have therefore been simply divided according to whether the disease was active or inactive at the time of the test.

Table X shows that the proportion of positive results in the active cases is significantly greater than in the inactive cases, though no less than 25 per cent. of the inactive subgroup were positive. The proportion of males and females in the subgroups is about the same.

TABLE X

RELATION OF TEST TO "ACTIVITY" OF DISEASE

Disease	Total		Male		Female		Positive					
							Total		Male		Female	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Active	517	80·6	138	77·6	379	81·7	247	47·8	88	63·8	159	42·0
Inactive ..	92	14·3	25	14·1	67	14·4	23	25·0	10	40·0	13	19·4
No Data ..	33	5·1	15	8·4	18	3·9	14	42·4	8	53·3	6	33·3
Total ..	642	100	178	100	464	100	284	44·2	106	59·6	178	38·4
Difference between Active and Inactive..							22·8±5·0		23·8±10·6		22·6±5·5	

COMMENT.—This analysis of the rheumatoid group reveals interesting clinical differences between the positive and negative cases. All but one of fourteen cases of rheumatoid arthritis associated with psoriasis, and 24 out of 25 cases in which only the central joints (joints other than the hands, feet, wrists and ankles) were affected were negative. It should also be noted that all of the six cases under the age of 15 were negative.

On the other hand, there was a marked predisposition for cases of rheumatoid arthritis with subcutaneous nodules to give a positive result in the test. This tendency was present in both males and females, 86·0 per cent. of males and 71·7 per cent. of females with subcutaneous nodules being positive; whereas, in cases without nodules, positive results were obtained in only 52·4 per cent. of males and 34·3 per cent. of females.

These observations suggest that the rheumatoid arthritis group is not completely homogeneous. A positive reaction appears to be particularly associated with what is usually regarded as the typical case—a chronic symmetrical polyarthritis affecting principally the peripheral joints and presenting clinical evidence of fibrinoid connective tissue such as subcutaneous nodules. When strict diagnostic criteria are applied, the proportion of rheumatoid cases giving a positive reaction is much higher than might be expected from the findings reported above. Thus, in 1951, 67·2 per cent. of 61 cases of rheumatoid arthritis, which were carefully selected for therapeutic studies in the Manchester Royal Infirmary, were positive—as against 44·2 per cent. cases of rheumatoid arthritis in the present series. The varied results reported by different workers using the same technique (Jawetz and Hook, 1949; Dordick and Wasserman, 1950) may indeed be partly explained by variations in the range of clinical syndromes diagnosed as "rheumatoid arthritis".

The finding that the rheumatoid agglutinating factor in diagnostic titres is associated with the occurrence of fibrinoid connective tissue raises the interesting question of the possible relationship of abnormal serum components to the altered

tissues present in fibrinoid. It was felt that the agglutinating factor might be an auto-antibody, especially in view of the report of Zoutendyk and Gear (1950), who found auto-antibodies in a case of disseminated lupus erythematosus in which fibrinoid connective tissue commonly occurs and the agglutination test is frequently positive. However, in a few cases of rheumatoid arthritis, some of which were positive in the agglutination test, I have been unable to obtain a positive direct Coomb's test, which suggests that auto-antibodies are not regularly present.

Provided the sensitized sheep cell suspension is sufficiently sensitive, the agglutinating factor can be demonstrated in low titre in the serum of many normal subjects or patients with diseases other than rheumatoid arthritis (*vide infra*). This is not to say that the factor appearing in high titre in rheumatoid arthritis is identical with that occurring in low titre in non-rheumatoid conditions. On the other hand, it may be that the mechanism responsible for the appearance of the factor in high titre in rheumatoid arthritis occurs in a mild form in other diseases and in apparently normal subjects. This possibility accords with the well-known fact that fibrinoid connective tissue may occur, though relatively inconspicuously, in a variety of pathological states unrelated to arthritic disease, and may indeed be produced in some normal animals by mild trauma (Klemperer, 1950). The variations in the titre of the agglutinating factor in human serum may, then, be merely an expression of differences in the severity or frequency with which a fairly common biological process occurs. Connective tissue changes histologically similar to those of rheumatoid arthritis are also found in rheumatic fever, in which the agglutination test was uniformly negative. However, the fibrinoid lesions of rheumatic fever are typically transient and generally of smaller amount than those occurring in rheumatoid arthritis—differences which may explain the results in rheumatic fever in the agglutination test. On the other hand, although the fibrinoid found in various diseases is microscopically similar, there may be qualitative differences undetectable by histological techniques; and if, in fact, the agglutinating factor is closely linked with the occurrence of fibrinoid connective tissue, the varied results obtained in the agglutination test in syndromes such as rheumatic fever, disseminated lupus erythematosus, rheumatoid arthritis, and periarteritis nodosa may reflect these qualitative differences.

Positive results were obtained in a significantly higher proportion of males than of females. The proportion of cases giving a positive result also increased sharply with the duration of the disease, and to a less extent with the degree of activity and joint involvement. It was shown that females generally had a longer clinical history, but that males and females were closely similar as regards the degree of radiological abnormality, the extent of joint involvement, and the activity of the disease. Hence the difference between the proportions of males and females giving a positive result cannot be explained by the different distribution of these factors in the sexes. More males than females had subcutaneous nodules; but if we give the female group the male distribution of this factor and recalculate the expected number of positive results in females, the difference between the proportion of male and female positives remains highly significant statistically. Factors other than those considered in this study must therefore be looked for to account for the difference between the sexes detected by the agglutination test.

Effect of Increasing Sensitivity of Test

The proportion of cases of rheumatoid arthritis giving a positive result also varies with the sensitivity of the test; it was shown (Ball, 1950) that the sensitivity could be increased by reading the result after 18 hrs' incubation rather than after one hour, or by increasing the concentration of anti-sheep rabbit serum used to sensitize the sheep cells. When either of these methods is adopted, the agglutinating factor can be demonstrated in the sera of many normal subjects and patients with other diseases. Hence some arbitrary titre must be chosen to define a positive result.

When, in the whole series of 1,943 cases, the test was read after 18 hrs' incubation, positive results were obtained in 50·4 per cent. of the rheumatoid group as compared with 44·2 per cent. with the " standard " method; but the proportion of false positive results was also increased from 2·5 per cent. to 4·2 per cent.

In another experiment, the concentration of anti-sheep rabbit serum was increased to the practicable limit (a concentration slightly below that at which spontaneous agglutination occurred), and 245 cases in the rheumatoid arthritis group and 332 of the control cases were tested. By this highly sensitive method positive results were obtained in 69·4 per cent. of the rheumatoid group, but 9·0 per cent. of the control cases were also positive. Most of the additional false positive reactions occurred in cases of arthritic disease, though, occasionally, apparently healthy subjects also gave a positive reaction. The additional positive cases in the rheumatoid group had minimal positive titres; they thus form an intermediate group between cases defined as positive or negative by less sensitive methods.

Even with a highly sensitive test, many patients diagnosed as suffering from rheumatoid arthritis show less agglutinating activity than some normal subjects and some patients with other diseases.

These results suggest (*a*) that increased sensitivity is accompanied with some loss in specificity, and (*b*) that in respect of the agglutinating factor there is some overlap between normal subjects, patients with rheumatoid arthritis, and patients with other diseases. But many patients suffering from rheumatoid arthritis possess the agglutinating factor in " titres " great enough to enable a diagnostic test to be devised; and when applied at a suitable sensitivity level the test clearly emphasizes certain similarities and differences known to occur in the rheumatic diseases.

Relation of Test to Clinical Course and Effects of Gold, ACTH, and Cortisone Therapy

Strongly positive results occurred in patients with a normal erythrocyte sedimentation rate, and the test was sometimes negative when the sedimentation rate was greatly increased. In serial tests, variations in the agglutinin titre bore no close relation to changes in the erythrocyte sedimentation rate.

A number of cases under gold treatment were serially tested, in some from the beginning of treatment or earlier, in others from a later stage. In those cases in which a definite remission followed gold treatment and in those which failed to improve, the result of the test sometimes remained unchanged. In cases in which the reaction changed from positive to negative or *vice versa*, no close association between the clinical state and the result of the test was noted.

Tests were performed on nine patients before, during, and after treatment with ACTH and/or cortisone for periods of up to 2 months. In all but two, no significant change in the agglutinin titre was noted. In the two exceptional cases, a definite fall in the agglutinin titre lasting 2 to 3 weeks occurred after 10 to 14-day courses of ACTH therapy; thereafter the titre rapidly rose to the levels obtaining before and during treatment. It was concluded that the agglutination test fails to reflect variations in the clinical state, and that ACTH and cortisone in therapeutic doses have no definite effect on the agglutinin titre.

Summary

Analysis of the results of a modified sheep cell agglutination test in 1,943 cases showed that:

(1) Positive results were obtained in the first test in 44·2 per cent. of 642 cases of rheumatoid arthritis, and in 2·5 per cent. of 1,301 control cases.

(2) Additional positive cases, especially in the rheumatoid group, were detected by repeatedly testing sera at intervals.

(3) A wide variety of non-arthritic diseases—including ankylosing spondylitis, gout, osteo-arthritis, rheumatic fever, and various bacterial arthritides—gave almost uniformly negative results, but disseminated lupus erythematosus was indistinguishable from rheumatoid arthritis in the test.

A detailed study of the 642 rheumatoid cases revealed that:

(1) Rheumatoid arthritis associated with psoriasis, and rheumatoid arthritis affecting only joints other than those of the hands, feet, wrists, and ankles, very rarely gave a positive reaction.

(2) A significantly higher proportion of males than of females were positive, and this could not be explained on the different distribution in the sexes of various clinical features such as age at onset, and duration and severity of disease.

(3) The proportion of positive results increased with the duration of the disease, but many cases with no radiological abnormality or a clinical history of up to only 6 months were positive.

(4) There was a strong association in both sexes between the occurrence of a positive result and the presence of subcutaneous nodules. The possible significance of this finding is discussed.

(5) Positive results were obtained in many inactive cases. In patients under gold, ACTH, or cortisone therapy, the test failed to reflect changes in the clinical state.

(6) The sensitivity of the test could be increased, though only at the cost of some loss in specificity.

It is concluded that the test is highly specific for rheumatoid arthritis and that it may be of value in distinguishing this syndrome from other arthritic diseases.

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Épreuve d'agglutination des globules rouges de mouton dans l'arthrite rhumatismale. Étude clinique et sérologique

RÉSUMÉ

L'analyse des résultats de l'épreuve d'agglutination des globules rouges de mouton, modifiée, dans 1,943 cas montra que:

(1) La première épreuve donna des résultats positifs dans 44,2% des 642 cas d'arthrite rhumatismale et dans 2,5% des 1,301 témoins.

(2) Des cas positifs additionnels, surtout parmi les rhumatisants, furent décelés au cours des épreuves sérologiques subséquentes.

(3) Dans des maladies très diverses, avec ou sans atteinte articulaire—y compris la spondylite ankylosante, la goutte, l'ostéoarthrite, le rhumatisme articulaire aigu, et de différentes arthritides bactériens—les résultats furent presque uniformément négatifs, mais l'épreuve ne distinguait pas entre le lupus érythémateux disséminé et l'arthrite rhumatismale.

L'étude détaillée des cas de rhumatisme révéla que:

(1) L'arthrite rhumatismale associée au psoriasis, et l'arthrite rhumatismale frappant seulement les articulations autres que celles des mains, des pieds, des poignets, et des chevilles, ne donnait que rarement une réaction positive.

(2) La proportion des résultats positifs était nettement plus grande chez les hommes que chez les femmes, ce qui ne peut pas s'expliquer par la distribution différente entre les sexes de divers caractères cliniques, tels que l'âge du début, la durée, et la gravité de la maladie.

(3) La proportion des résultats positifs augmentait avec la durée de la maladie, mais on en trouvait chez beaucoup de malades qui ne présentaient pas d'anomalies radiologiques ou dont l'histoire clinique ne remontait pas à plus de six mois.

(4) Il y avait une association étroite dans les deux sexes entre les résultats positifs et la présence de nodules souscutanés. On discute la probable importance de ce fait.

(5) On obtint des résultats positifs dans beaucoup de cas inactifs. Chez les malades traités par des sels d'or, par l'ACTH, ou par la cortisone, l'épreuve ne reflèta pas les changements de l'état clinique.

(6) On pourrait rendre l'épreuve plus sensible, mais sa spécificité en souffrirait un peu.

(7) On conclut que cette épreuve est très spécifique de l'arthrite rhumatismale et qu'elle est utile pour distinguer entre ce syndrome et les autres affections arthritiques.

Prueba de aglutinacion de eritrocitos de carnero en la artritis reumatoide. Estudio clínico y de laboratorio

SUMARIO

El análisis de los resultados de la prueba de aglutinación de eritrocitos de carnero, modificada, en 1,943 casos mostró que:

(1) La primera prueba dió resultados positivos en el 44,2% de 642 casos de artritis reumatoide y en el 2,5% de 1,301 testigos.

(2) Más casos positivos fueron hallados después de exámenes serológicos repetidos.

(3) En enfermedades muy diversas, con o sin implicación articular—incluído la espondilitis anquilosante, la gota, la osteoartritis, el reumatismo poliarticular agudo, y varios artritides bacterianos—los resultados fueron casi uniformemente negativos, pero la prueba no distinguía entre el lupus eritematoso diseminado y la artritis reumatoide.

El estudio detallado de los casos reumatoides reveló :

(1) Artritis reumatoide asociada con psoriasis, y artritis reumatoide que implicaba sólo

articulaciones otras que las de las manos, pies, muñecas y tobillos, motivaban muy raramente una reacción positiva.

(2) La proporción de resultados positivos era netamente mayor en los hombres que en las mujeres, lo que no se puede explicar por la distribución diferente en cada sexo de varios carácteres clínicos, como la edad de comienzo, la duración y la gravedad de la enfermedad.

(3) La proporción de los resultados positivos aumentaba con la duración de la enfermedad, pero los hubo también en muchos enfermos sin anomalías radiológicas o en aquellos con una historia clínica de seis meses o menos.

(4) Hubo una asociación estrecha en ambos sexos entre los resultados positivos y la presencia de nódulos subcutáneos. Se discute la importancia probable de este hecho.

(5) Resultados positivos fueron obtenidos en muchos casos inactivos. En enfermos tratados con sales de oro, ACTH, o cortisona, la prueba no reflejó las variaciones del estado clínico.

(6) Se podría aumentar la sensibilidad de la prueba, pero su especifidad sufriría un poco.

(7) Se conclude que esta prueba es muy específica para la artritis reumatoide y que podría utilizarse para diferenciar entre este síndrome y otras enfermedades artríticas.

INTRA-ARTICULAR HYDROCORTISONE (COMPOUND F) ACETATE*
A PRELIMINARY REPORT

BY

C. R. STEVENSON,† J. ZUCKNER,‡ and R. H. FREYBERG

From the Hospital for Special Surgery, and Cornell University Medical College, New York

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The suppression of inflammation in the joint structures of patients with rheumatoid arthritis by cortisone acetate administered systemically is well known. Hydrocortisone acetate, formerly known as Compound F acetate (17-hydroxy-corticosterone-21-acetate), administered orally or intramuscularly, has recently been shown to have a similar suppressive effect upon this inflammation (Ward and others, 1951; Freyberg, Stevenson, Traeger, and Zuckner, 1952). One of the most important objections to the systemic use of these steroids is that amounts adequate to produce a beneficial effect may cause undesired physiological changes of hyperadrenocorticalism.

Thorn (1951) is reported to have been the first to inject hydrocortisone acetate into an inflamed joint of a patient with rheumatoid arthritis with improvement in the inflammation. Hollander and others (1951) reported sustained local benefit and no systemic effect, after intra-articular injections of hydrocortisone into patients with various illnesses including rheumatoid arthritis. They reported no objective improvement after intra-articular injections of cortisone acetate. Other workers have demonstrated that cortisone acetate injected directly into an inflamed joint produces local improvement which is manifested clinically and by changes in the synovial fluid without producing a significant systemic effect (Freyberg and others, 1951). After repeated intra-articular injections of cortisone acetate, however, the response in most patients becomes less. In a few others this material seemed to be irritating as shown by worsening of the inflammation at the joint treated and an increase in the number of cells in the synovial fluid.

The present study deals with clinical and synovial fluid changes observed after intra-articular injections of hydrocortisone acetate in patients with rheumatoid arthritis.

Procedure

Hydrocortisone acetate was supplied for this investigation§ in two forms: the usual aqueous suspension (25 mg. per 1·0 ml.) containing Tween-80 and butyl alcohol, and also the dry crystalline state. The crystalline material was studied to determine whether any of the effects observed with the usual suspension were produced by any of its components apart from the steroid. The physical instability and uneven suspension of the

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† Schering Research Fellow in Rheumatic Diseases.

‡ Merck Research Fellow in Rheumatic Diseases.

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crystalline steroid in water made this preparation difficult to work with, and most of the studies were done with the regular suspension.

The steroid was injected into the knee joint in all patients except one in whom it was injected into the elbow. The skin was routinely prepared for injection by thorough washing with green soap, removal of the soap with ether, and application of tincture of thimerosal* which was then removed with alcohol. The needle was inserted into the knee joint by the medial sub-patellar approach, using a solution of 1 per cent. procaine for local anaesthesia. If a large quantity of fluid was to be aspirated, a 20-gauge needle was used; for steroid injection only, a 24-gauge needle was satisfactory. The first intra-articular injection of hydrocortisone acetate in each patient was to 25 mg. or less, in order to minimize undesirable effects in the event of a local intolerance to the drug. The largest amount injected at any time in these patients was 75 mg. An effort was made to maintain a decrease of at least 50 per cent. of pain and stiffness at the joint treated. The interval between injections, and, in some patients, the size of the dose, was usually determined by the patient's subjective response, especially the reduction of pain. When there was poor response injections were given more frequently or the size of the dose was increased. Objective changes were noted, but these did not influence the size of the dose or frequency of injection, since no attempt was made to effect any certain degree of objective improvement. The first two to four injections were usually given at 3- to 7-day intervals to maintain the desired effect; later the interval could be lengthened to several weeks in many cases. The average interval between injections (the number of treatment days divided by the total number of injections) varied from 3 to 29 days.

Cells in the synovial fluid were counted within 1 or 2 hours of the removal of the fluid. The differential cell count was made from smears stained with Wright's technique; whenever possible, a total of 100 cells was counted on each slide.

The patients were examined at frequent intervals after the course of injections had been begun and their clinical progress was observed for several weeks after the injections were discontinued—in two patients for as long as 100 days.

Results

Thirteen patients with rheumatoid arthritis received 96 intra-articular injections of hydrocortisone acetate into twenty different joints. All of these patients tolerated the local injections of the steroid very well, in contrast with other series of patients treated with intra-articular cortisone acetate in whom a temporary increase of joint inflammation was occasionally noted.

There was no difference between the clinical results with hydrocortisone acetate in water and those with the standard suspension. All patients reported some degree of prolonged local benefit. In some the relief of pain was apparent immediately after withdrawal of the injecting needle; in others the relief was delayed for approximately 12 to 18 hours. It is possible that the immediate pain relief noted by some patients was caused by the unintentional injection of procaine into the joint at the time of the intra-articular injection of hydrocortisone acetate.

A detailed analysis of results is presented in the Table, where the severity of synovitis at the joint injected is expressed as a composite estimate (graded 1 to 4) of the signs of inflammation, including abnormal local heat, swelling, synovial fluid, capsular thickening, tenderness, and impaired function. Subsequent objective improvement was graded by the degree of change in these same signs evaluated by the same observer. Subjective improvement represents the degree of relief from discomfort and disability compared with the pre-injection symptoms. The average

* Merthiolate.

Patient	Sex	Joint Injected	Severity of Synovitis before Treatment (Grade)	Average Improvement %		Injections					rage erval ween tions ys)
				Subjective	Objective	25 mg.	50 mg.	Other Doses (mg.)	Total Amount (mg.)	Total Number	
R.C.	F	R. knee L. knee	1 to 2 2	60 65	40 60	3 7	5 1		325 225	8 8	·8 ·5
F.S.	F	L. knee	3	85	90	4			100	4	·3
I.H.	F	R. knee L. knee	2 3	70 60	50 30	3 4	 6		75 400	3 10	·0 ·1
E.R.	F	R. knee	4	80	80	2	2		150	4	·5
R.J.	M	R. knee	2	70	25	3			75	3	·7
M.F.	F	R. knee L. knee	2 3	50 60	50 60	2	3 4	2 of 75	350 200	7 4	·4 ·5
E.B.	F	L. knee	2	70	70	1	6		325	7	·4
T.E.	F	R. knee L. elbow	1 2	90 0	30 0	1 1	3	1 of 6·25	175 31·25	4 2	·8 ·0
E.H.	F	R. knee L. knee	1 1	50 45	25 25	1 1	2 3		125 175	3 4	·3 ·5
F.H.	F	L. knee	2	30	40	2	1	2 of 75	250	5	·8
J.H.	M	R. knee L. knee	1 2	35 50	90 10	1 2	2		125 50	3 2	·3 ·0
A.S.	M	R. knee	2	10	10	1	3		175	4	·0
B.H.	F	R. knee L. knee	2 2	30 50	40 50	1 3	2 4		125 275	3 7	·3 ·1

* Westergren method. † Not determined. ‡ No fluid obtainable.

re than

improvement refers to conditions prevailing during the greater part of the period when injections were given.

Subjective improvement estimated at 70 per cent. or more was reported to occur in six of the twenty joints injected, and symptomatic improvement estimated at 50 per cent. or more was reported in fourteen joints. The clinical estimation of objective improvement of 70 per cent. or greater was observed in four joints, and of 50 per cent. or more in nine joints. Objective improvement was equal to or greater than the reported subjective improvement in half the cases. No objective change was seen until 3 to 14 days after subjective improvement was reported.

Some patients could detect no change in the injected joint until after three or four injections at close intervals; others noticed persistent partial relief from pain

OCORTATE IN PATIENTS WITH RHEUMATOID ARTHRITIS

Total Number	rage erval ween tions ys)	Joint Fluid Cytology				Erythrocyte Sedimentation Rate*		Comment
		Pre-treatment		Post-treatment				
		WBC	PMN ** %	WBC	PMN ** %	Pre-treatment	Lowest Post-treatment	
8	6·8	10,900	73	4,100	25	53	15	
8	6·5	19,700	77	3,100	38	§	—	
4	8·3	19,850	70	2,500	10	46	40	Receiving gold salt with unsatisfactory improvement of joint later injected; 96 days since last injection of hydrocortisone acetate.
3	9·0	8,400	86	2,900	22	78	61	
0	9·1	15,950	77	550	12	§	—	
4	5·5	N.D.†	—	—	—	31	42	Receiving gold salt therapy with incomplete suppression of disease.
3	6·7	N.F.O.‡	—	—	—	N.D.†	—	Receiving insulin for diabetes mellitus; glycosuria unchanged.
7	1·4	23,350	62	50	18	§	—	Treated during relapse after withdrawal of cortisone acetate given orally.
4	9·5	7,500	40	2,300	2	§	—	
7	9·4	4,200	46	50	0	94	72	
4	5·8	N.F.O.‡	—	—	—	78	75	
2	7·0	N.F.O.‡	—	—	—	§	—	
3	8·3	N.F.O.‡	—	—	—	40	33	Receiving gold salt with unsatisfactory improvement.
4	1·5	N.F.O.‡	—	—	—	§	—	
5	8·8	22,500	68	2,400	3	91	84	
3	1·3	2,500	49	2,300	48	11	15	Receiving 75 mg. cortisone acetate daily orally with only partial improvement of injected joints.
2	1·0	N.F.O.‡	—	—	—	§	—	
4	3·0	7,800	54	3,500	11	N.D.†	—	
3	9·3	29,400	68	N.D.†	—	95	81	Untreated joints became worse.
7	7·1	36,650	95	5,800	62	§	—	

re than one joint received treatment with hydrocortisone acetate simultaneously. ** Polymorphonuclear leucocytes.

immediately after the first injection of only 25 mg. hydrocortisone acetate. There was no apparent correlation between the measurable severity or duration of joint inflammation and the speed or degree of response to any specific dose.

In every instance in which it could be obtained for study the synovial fluid showed a decrease in the total number of cells and in the polymorphonuclear cell percentage after injection of hydrocortisone acetate. Early in the investigation, when joint fluid was present in abnormal amounts, an amount equal to the volume of hormone injected was usually aspirated. As the study progressed it was noted that joints from which *all* readily available fluid was aspirated almost always showed a better response. This then became the standard procedure. Gross blood in the synovial fluid was detected in approximately 20 per cent. of the aspirations; this was

considered to be caused by trauma from the needle. Bloody fluid was usually obtained only towards the end of the aspiration of a large volume of fluid.

In four of nine patients the erythrocyte sedimentation rate decreased by more than 10 mm. per hour.

Discussion

The available evidence indicates that the primary site of action of hydrocortisone acetate injected intra-articularly is in the structures of the injected joint. Among our patients there was no instance of improvement in uninjected joints occurring simultaneously with improvement in the treated joint. Joints that were not injected did not change in most patients; in a few patients with synovitis in two or more weight-bearing joints, the untreated joints became worse. For example, improvement in an injected knee joint was sometimes accompanied by the worsening of an ipsilateral untreated arthritic ankle or hip joint. This probably resulted from the increased weight bearing permitted by the improvement in the treated joint.

No explanation is known to us for the prolonged benefit sometimes seen after an intra-articular injection of hydrocortisone acetate.

The changes in the erythrocyte sedimentation rate which occurred during the course of intra-articular injections might have resulted from improvement in the synovitis of injected joints when this constituted the major portion of the recognizable articular inflammation. In several patients with involvement of only a few small joints in addition to the one injected, the sedimentation rate became normal when the injected joints improved.

It is fully appreciated that intra-articular use of hydrocortisone acetate in patients with rheumatoid arthritis is merely a local treatment for a systemic disease. It is not proposed as a substitute for good systemic treatment, but there are several situations in which intra-articular injection of this hormone may prove to be of considerable practical value. A patient with rheumatoid arthritis may have only a few joints affected, most of which might logically be injected. It might also be considered as an adjuvant to therapy when one joint predominates as the chief source of pain and disability. Cases F.S. and E.R. (Table) are examples of patients with rheumatoid arthritis who were practically incapacitated by severe inflammation of one knee that was slow to respond to gold therapy, and both were able to walk after hydrocortisone acetate had been injected. Another condition in which local treatment could be preferable to systemic treatment is demonstrated in the case of R.J., a patient with diabetes requiring 40 units of insulin daily. It was felt that systemic cortisone or corticotropin would be unwise because of the diabetic state; after trial of many accepted forms of treatment, without notable success, the intra-articular injection of hydrocortisone acetate produced a significant improvement in the knee that had been partially incapacitating the patient. The diabetes was not measurably affected.

In most instances the amounts of the steroid used for each injection were arbitrarily selected. Further experience may indicate more precisely the optimal dose that should be used as well as the interval at which injections should be given. In such a study extending over long periods of time, one must realize that the severity of the disease may change spontaneously by some means not related to the treatment.

The true value of intra-articular hydrocortisone acetate and the details of treatment can be determined only after extended observation of many patients.

Apart from the more obvious disadvantages of repeated injections into an inflamed joint, the possibility of accidental infection, and resultant pyarthrosis, must always be remembered. Experience has shown that cortisone acetate may considerably modify the clinical signs of infection (Ward and others, 1950). Because hydrocortisone acetate exerts a suppressive effect on inflammation very similar to that of cortisone acetate it is reasonable to consider that a high concentration of hydrocortisone acetate in the tissues might alter local tissue response so that the manifestations of infection might not be recognized at an early stage.

Summary

Altogether 96 injections of hydrocortisone acetate were made into twenty joints of thirteen patients with rheumatoid arthritis and all were well tolerated. Some degree of symptomatic improvement was reported by all patients. Objective improvement of 50 per cent. or more occurred in nine joints. The interval between injections at each joint varied from 3 to 29 days (average 13·8 days).

The following conclusions were reached:

(1) Hydrocortisone acetate injected into an inflamed joint of a patient with rheumatoid arthritis is capable of producing local subjective and objective improvement.

(2) This procedure is now reported as an experimental study, but may prove of significant clinical value in carefully selected cases.

(3) Further investigation is needed to establish the practicability of the intra-articular use of hydrocortisone acetate, and to assess its long-term effect upon inflamed joint structures and upon the course of the disease.

The technical assistance of Miss Joan Kline is gratefully acknowledged.

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Expériences avec l'acétate de hydrocortisone (Composé F) intra-articulaire
Rapport préliminaire

RÉSUMÉ

On effectua en tout 96 injections d'acétate de hydrocortisone dans 20 articulations de 13 malades atteints d'arthrite rhumatismale; toutes les injections furent bien supportées. Tous les malades accusèrent une amélioration symptomatique. Une amélioration objective de 50% ou plus se produisit dans neuf articulations. L'intervalle entre les injections dans la même articulation était de 3 à 29 jours (13,8 en moyenne).

On arriva aux conclusions suivantes:

(1) L'acétate de hydrocortisone injecté dans une articulation enflammée d'un arthritique rhumatisant est capable de produire une amélioration subjective et objective.

(2) Ce procédé, rapporté ici à titre d'étude expérimentale, peut acquérir de l'importance clinique dans des cas soigneusement choisis.

(3) Des recherches ultérieures sont nécessaires pour déterminer la valeur pratique des injections intra-articulaires d'acetate de hydrocortisone et pour évaluer leur effet éloigné sur les tissus articulaires enflammés et sur l'évolution de la maladie.

Experimentos con acetato de hidrocortisona (Compuesto F) intra-articular
Informe preliminar

SUMARIO

Acetato de hidrocortisona fué inyectado 96 veces en total en 20 articulaciones de 13 enfermos con artritis reumatoide; todas las inyecciones fueron bien toleradas. Todos los enfermos acusaron mejoría sintomática que fué, objetivamente, de 50 o más por ciento en enuve articulaciones. El intervalo entre las inyecciones en las mismas articulaciones fué de 3 a 29 días (13,8 de término medio).

Se llegó a las conclusiones siguientes:

(1) Acetato de hidrocortisona inyectado en una articulación inflamada de enfermo con artritis reumatoide es capaz de producir mejoría subjetiva y objetiva.

(2) Este procedimiento, referido aquí como estudio experimental, puede adquirir importancia clínica en casos cuidadosamente escogidos.

(3) Se necesita investigaciones ulteriores para determinar el valor práctico de las inyecciones intra-articulares de acetato de hidrocortisona y para apreciar su efecto remoto sobre estructuras articulares inflamadas y sobre la evolución de la enfermedad.

CORTISONE - ASCORBIC ACID INTERACTION AND THE PATHOGENESIS OF AMYLOIDOSIS*†

MECHANISM OF ACTION OF CORTISONE ON MESENCHYMAL TISSUE

BY

GUNNAR TEILUM

From the Laboratory for Rheumatic Research, University Institute of Pathological Anatomy, Copenhagen

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The experiments to be reported here show that under certain conditions a few injections of cortisone into animals result in the prompt appearance of amyloid in the spleen or other organs; they indicate that the mechanism whereby the hormone of the adrenal cortex maintains the structure and function of mesenchymal tissue in general is an *indirect* one, mediated by ascorbic acid. Well-defined structural and functional phases in the natural diseases and in the experimental disorder of the mesenchyma—which may in some way be associated with a disturbance of some enzyme system (ribonuclease, hyaluronidase)—seem to be controlled by an *interaction* of a hormone of the adrenal cortex of cortisone type with ascorbic acid.

These findings offer an approach to the elucidation of the following points:

(*i*) *The pathogenesis of amyloidosis*, including the origin of amyloid in rheumatoid arthritis,

(*ii*) *Certain apparently antagonistic effects of cortisone and ascorbic acid* on mesenchymal tissue,

(*iii*) *The mechanism of action of cortisone and ascorbic acid* on mesenchymal tissue in general.

The causation and mechanism of the formation of amyloid is still considered to be very much of a mystery, and though many different theories have been put forward in rapid succession, it has been impossible to establish a common denominator for the formation of amyloid in the series of varying conditions in which it has been observed in human as well as in experimental studies.

An old theory was that amyloid was formed when chondroitin-sulphuric acid, released from the breaking down of cartilage or elastic tissue, was combined with protein. Loeschcke (1927) looked upon amyloid as an insoluble precipitate of antigen and antibody. It has been generally believed that amyloid is an infiltration rather than a degeneration.

The protein content of amyloid has for a long time suggested that some abnormality of the protein metabolism is involved, and conditions in which secondary amyloidosis may develop are often associated with hyperglobulinaemia. The

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morphogenetic relations of hyalinosis, amyloidosis, and paramyloidosis in mesenchymal disease associated with hyperglobulinaemia and accumulations of plasma cells in the active phase have recently been studied in detail (Teilum, 1948a, b; 1949).

The association of amyloidosis and rheumatoid arthritis is rare (Hench and others, 1948). Unger and others (1948) found amyloidosis in four out of 58 cases examined *post mortem*, and in the Congo red test in six out of 56 patients. In a series of *post-mortem* examinations comprising about 100 cases of rheumatic and pararheumatic disease we have found an astonishingly high incidence of amyloidosis in rheumatoid arthritis (Teilum and Lindahl, 1952) in the Laboratory for Rheumatic Research. Amyloid deposits, most frequently present in kidney, spleen, and adrenal glands, could be demonstrated in twenty out of 32 cases (Table I). The changes were pronounced in eleven cases, but milder degrees were revealed by means of methyl violet stain for amyloid in the other nine cases. The occurrence of milder or severer degrees of amyloid deposition was thus found to be a highly characteristic lesion in rheumatoid arthritis, and presumably one of the most frequent causes of amyloid formation in general.

TABLE I

INCIDENCE OF AMYLOID LESIONS IN 32 CASES OF RHEUMATOID ARTHRITIS
(after Teilum and Lindahl, 1952)

Grade	No.	Site	No.
Advanced	8	Kidneys	15 (inc. 9 adv. or mod.)
Moderate	3	Spleen	16
Mild	9	Adrenals	5
Total cases	20		

Experimentally, amyloidosis has been produced by various means, including repeated parenteral administration of protein foreign to the species, repeated injections of antigen, bacteria, casein, sodium caseinate, pentose, nucleotides, human serum, sulphur, etc., and it has also been found in tumour-bearing mice. Recently Pirani and others (1949) demonstrated amyloid in guinea-pigs fed on scorbutogenic diets for 8 weeks or longer. Six out of seven animals of this group showed distinct amyloidosis, and in those showing amyloid deposition the spleen was severely involved, the liver moderately, and the adrenal cortex only minimally in few cases. According to these authors, their observations do not warrant any positive conclusion as to the possible role of ascorbic acid or inanition in the pathogenesis of amyloid deposition, but they point out that amyloidosis has not been produced previously in animals by means of a deficient diet.

Variability in staining reactions suggests that amyloid is not a uniform chemical substance, but a series of closely-related protein compounds (Hass and others, 1943), the composition of which may vary from one case to another and in different areas within the same case. Letterer (1949), who studied the electrophoretic pattern of serum protein in amyloid mice, believes that the protein constituent of amyloid is not of a specific chemical nature, but a part of plasma protein, and in many cases the result of antigen-antibody reactions. Two processes appeared to be of importance: the disturbance of the colloidal stability of the plasma, and the formation of new plasma proteins of α, β, and γ types (Letterer, 1949).

Much uncertainty has surrounded the chemical nature of the amyloid substance,

but at the present time it is generally considered to be a *glycoprotein* in which a mucopolysaccharide (chondroitin sulphuric acid (Ehrström, 1939) or mucoitin monosulphuric acid (Meyer, 1947)) has been attached to a globulin.

Hass (1942) identified two slightly different protein fractions and a sulphate-bearing polysaccharide in secondary amyloidosis, and showed that from 1 to 2 per cent. of the amyloid molecule is of carbohydrate nature. It was concluded that amyloid has a matrix of protein which becomes complex by combination with various other substances of the body fluids.

In some cases Johansson and Wahlgren (1938) has found a metachromatic staining of amyloid with toluidine blue.

Experiments

Pyroninophilic Mesenchymal Cells and Origin of Hyaline and Amyloid.—A further elaboration of my previous studies on hyalinosis and amyloidosis in the glomeruli of the kidney, the spleen, and other organs in mesenchymal disorders also associated with hyperglobulinaemia and accumulations of plasma cells (Teilum, 1948-49), shows that cytoplasmatic pyroninophilia of reticulum cells and other mesenchymal derivative cells represents a common alteration in the early phase of mesenchymal disorder, which may result in the formation of hyaline or amyloid.

The findings are illustrated by the following examples of mesenchymal disease and by experiments in animals.

Sarcoidosis (Teilum, 1948a, 1949, 1951) pyroninophilic mesenchymal cells—in addition to an accumulation of typical plasma cells—were found scattered or accumulated in lungs, spleen, lymph nodes, and other organs, and the pyroninophilic substance showed all transitions to prehyaline and hyaline masses. The so-called stratified intracellular bodies in sarcoidosis were shown to be pyroninophilic in their early stage and were considered to be a biochemical product of mesenchymal cells related to the pronounced development of hyalinosis (Teilum, 1949). Hyaline or prehyaline glomerular lesions with the same pathogenesis and explaining the renal disease in sarcoidosis were later described (Teilum, 1951).

Pyroninophilic cells and giant cells with pyroninophilic inclusions in the lung were a common finding in generalized sarcoidosis. Sections from the same blocks were incubated with purified ribonuclease (10 mg.-100 ml.) at *p*H 6·7, or with buffer solution alone for 1 hour at 37° C. After treatment the sections were stained with pyronine-methyl-green and the incubated sections were compared with the untreated sections. After incubation the pyroninophilia of the cytoplasm of the different mesenchymal cell types was abolished.

Glomerulonephritis. Studies of sections from acute and subacute cases of glomerulonephritis and renal changes in paramyloid syndrome with hyperglobulinaemia (Teilum, 1948b) also revealed, in addition to plasma cells, pyroninophilic cells of the glomerular tufts (epithelial and endothelial), interstitial mesenchyma, adventitia of vessels, and vascular endothelium. All stages of transition from such cytoplasmatic changes to prehyaline, hyaline, or paramyloid substance were observed in different cases.

It was evident that formation of hyaline, amyloid, and related substances was always anticipated—in glomeruli, interstitium, vascular walls—by a *pyroninophilic precursor stage* of mesenchymal cells, representing a typical alteration in the *active phase*, which is also characterized by the accumulation of plasma cells in the spleen and other organs, and by a liberation of γ-globulin to the blood.

Teilum and others (1950) recently described a pronounced inhibitory effect of cortisone on accumulation of plasma cells in the spleen, as well as on pyroninophilic cells in the glomeruli of the kidney in experimental acute glomerulonephritis in rabbits hyperimmunized

for several months (1951). In the animals treated with cortisone, there was a marked rise in the α-globulin fraction and a less marked fall in γ-globulin. In the other series not so treated, the γ-globulin was elevated in those animals who had acute nephritis before treatment with cortisone was commenced, whereas the cases with a marked nephrotic syndrome showed an increase of α- and β-globulin fractions and decreased total protein (Teilum and others, 1951).

In the animals not treated with cortisone a more protracted transition can be seen

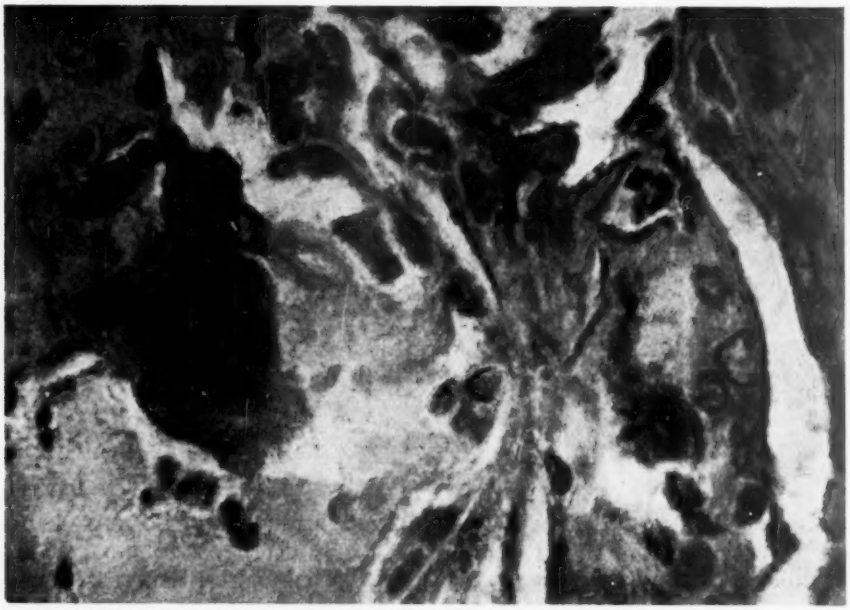


FIG. 1.—Transition from swollen pyroninophilic glomerular cells to a non-pyroninophilic homogeneous (pre-hyaline) substance. Hyperimmunized rabbit. Pyronin-methylgreen. ×950.

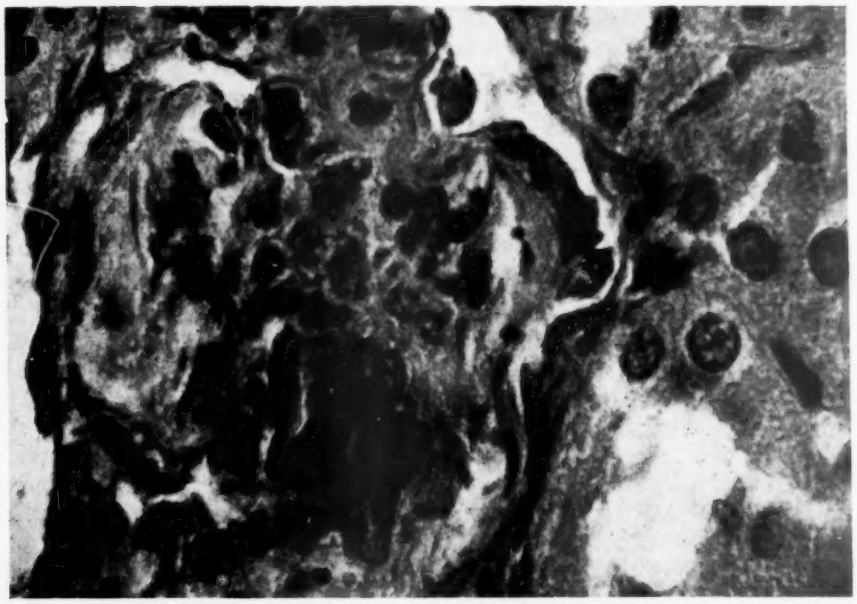
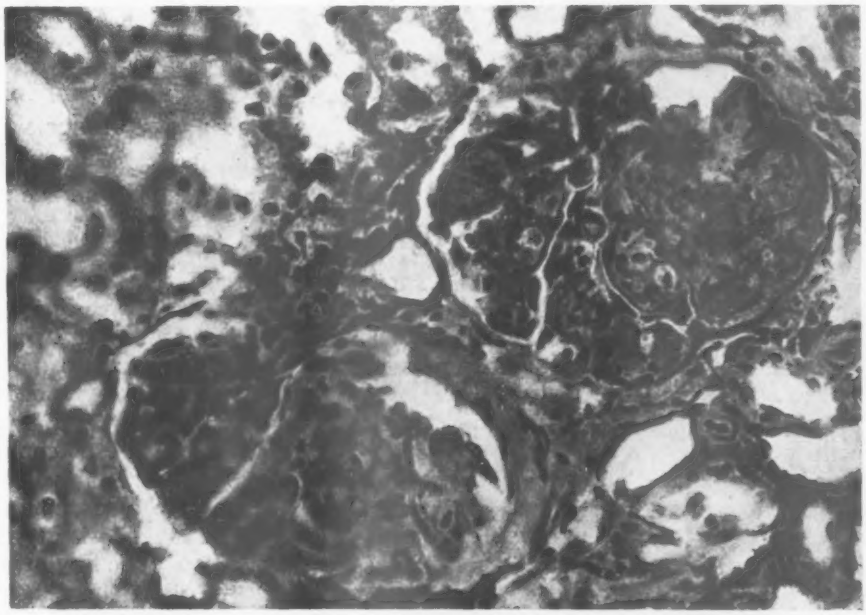


FIG. 2.—Pyroninophilic cells in epithelium of visceral and parietal capsule layer of the glomerulus. Note larger lump of nuclei surrounded by a pyroninophilic cytoplasmatic mass in centre. Hyperimmunized rabbit. Pyronin-methylgreen. ×950.

from swollen glomerular cells with blurred, highly pyroninophilic cytoplasm to a non-pyroninophilic pale homogeneous prehyaline or pre-amyloid substance (Fig. 1), whereas the administration of cortisone resulted in the prompt appearance of the last-mentioned phase. Fig. 2 shows pyroninophilic cells in the epithelium of the visceral and parietal capsular layer with swollen cytoplasm, and in glomerulus a larger lump of pyroninophilic cells with many nuclei, surrounded by an ill-defined blurred pyroninophilic cytoplasmatic mass. The pronounced pyroninophilia of the glomeruli rich in cells in experimental acute glomerulonephritis was also abolished by treatment with ribonuclease as described above (Figs 3 and 4).



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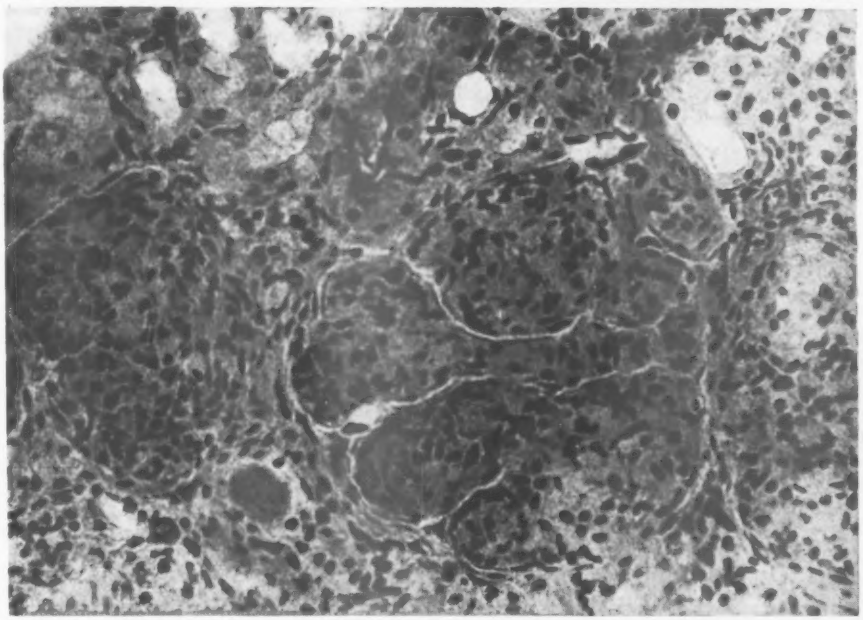

(4)

FIGS 3 and 4.—Sections from same block of experimental acute glomerulonephritis in rabbit. Pyroninophilia of cytoplasma of glomerular cells abolished after incubation with ribonuclease. (Cf. Fig. 4 with the untreated section, Fig. 3.) Pyronin-methylgreen. ×320.

Whilst the active (pyroninophilic) phase of mesenchymal disorder is thus linked with an increased production of cytoplasmatic protein (ribose nucleic acid) by reticulum cells and other mesenchymal derivative cells, which in natural disease —under the influence of controlling factors—will show regression in its further course with or without formation of hyaline (*hyalinosis*) representing an inactive phase of healing, a perverted phase in mesenchymal protein synthesis may, under certain circumstances, take place and result in the formation of amyloid (*amyloidosis*).

Effects of Cortisone in Producing Amyloidosis

Letterer (1926) and Bohle and others (1950) produced experimental amyloidosis in mice by means of repeated injections of sodium caseinate or of nucleic acid solution. The incidence of amyloidosis in such experiments seems, however, to be varying, and Hass and others (1943) failed to produce amyloidosis in mice which were given injections of a solution of sterile sodium caseinate.

Material and Methods.—In these experiments, female mice of the same C_3H-strain weighing from 20 to 25 g. were used. During the experiment and for the preceding 8 days, they were only given oatmeal and water. They then received 0·5 ml. of a 2 per cent. casein solution in 0·25 per cent. NaOH in daily hypodermic injections into the back. In the course of 3 weeks, three series of five injections were given with intervals of 2 days between each series, i.e. a total of fifteen injections in 21 days; this was followed by up to ten injections in the course of another 4 or 5 weeks. The first experiments comprised 160 mice. Some of these had, *in addition*, been given 0·3 mg. cortisone in hypodermic injections simultaneously with the casein injections for the purpose of examining the influence of this hormone on the development of experimental amyloidosis at various times in the course of treatment, the changes of the spleen were controlled by means of biopsy, made under ether anaesthesia through a laparotomy with ligation of the distal pole of the spleen. The animals were weighed three times a week. Blocks were taken from the spleen, kidneys, adrenals, and liver, being fixed in 10 per cent. neutral formalin and then embedded in paraffin. Sections were stained with hematoxylin-eosin, by Van Gieson's method, with toluidine blue, and by the Hotchkiss periodic acid routine, as well as by the Unna-Pappenheim pyronin-methyl-green method for pyroninophilia and the Congo red stain and methyl-violet stain (Eden) for amyloid.

Results.—After casein injections had been given for 3 weeks, biopsy of the spleen of seven subjects revealed no signs of amyloidosis. After 5 weeks, four other subjects treated with casein injections only showed no signs of amyloidosis of the spleen, whereas four of the cortisone-treated animals killed at this time displayed it to a marked degree.

Similarly, five casein-treated mice showed no amyloidosis 6 weeks after beginning the treatment, whereas five casein-cortisone-treated mice displayed marked amyloidosis of the spleen.

As these findings seemed to indicate that cortisone promoted the production of amyloid, eight casein-cortisone-treated mice and another eight mice treated with casein solution only were killed 8 weeks after beginning the treatment. In the latter group none showed signs of amyloidosis of the spleen, but only some reticulum cell proliferation, whereas all those in the former group showed marked amyloidosis of the spleen, and some showed rather less pronounced changes in liver and kidneys.

In another experiment, eight mice treated in advance with casein only for 6 weeks

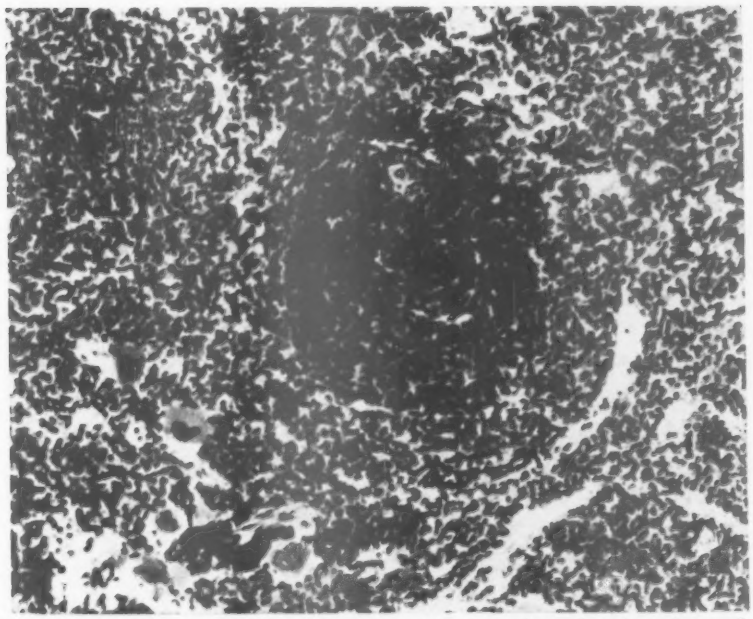

FIG. 5.—Biopsy of spleen in mouse treated with casein injections for 6 weeks and showing no signs of amyloidosis. Haematoxylin and eosin. ×160.

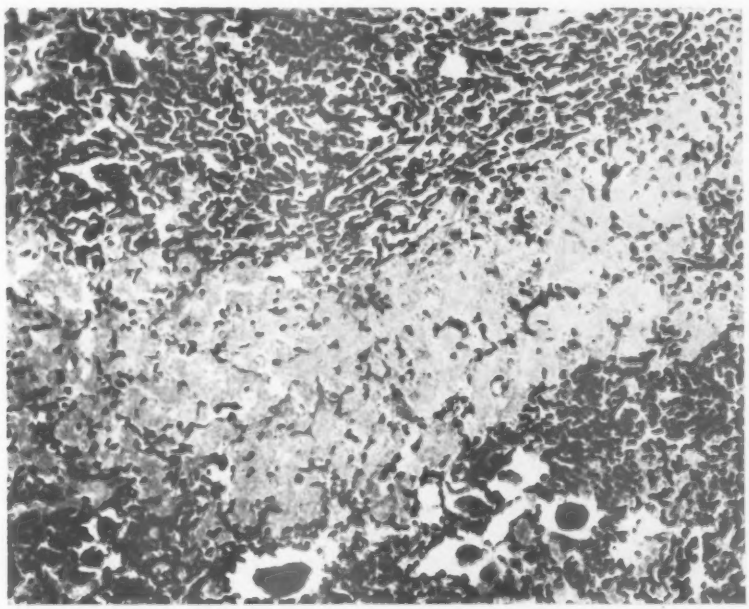

FIG. 6.—Marked amyloidosis in spleen of same animal as Fig. 5 after further administration of 0·3 mg. cortisone daily for 4 days. Haematoxylin and eosin. ×160.

displayed no signs of amyloidosis of the spleen at biopsy; four of these animals were then given 0·3 mg. cortisone daily for 4 days; they were then killed, and a very pronounced amyloidosis of the spleen produced by the few days' administration of cortisone (Figs 5 and 6) was found histologically at autopsy, whereas there were no amyloid deposits in the four animals not treated with cortisone.

Only two out of 22 casein-treated mice which had not been given cortisone

displayed pronounced amyloidosis in the spleen or in other organs 8 weeks after the casein injections were begun.

Daily injections of 0·3 mg. cortisone for 6 days did not cause amyloidosis in eight subjects not treated with casein in advance. Amyloidosis did not develop after administration of cortisone in animals treated with casein only 2 weeks in advance, but appeared in seven out of eight animals treated for one month.

A similar but essentially weaker and less constant amyloid-producing effect was found after the administration of ACTH (Acton) 0·5 mg. administered in two daily doses for 5 days to five mice.

The time of onset of the amyloid-producing effect of cortisone in relation to the beginning of the casein treatment shows some variations in the various series of experiments, but it is evident that the administration of cortisone resulted in the prompt appearance of amyloid in mice previously treated with injections of sodium caseinate for several weeks, though the casein had been insufficient to produce amyloidosis by itself.

In connection with the injection treatment, some of the subjects developed ulcerations and necroses around the site of injection, and in a few of the experiments there was quite a high mortality among the animals, which often showed a very poor resistance.

After a few weeks' casein injections the spleen showed accumulations of pyroninophilic reticulum cells, including numerous plasma cells and pyroninophilic giant cells with irregular arrangement of the nuclei. The cortisone treatment caused a depression of the pyroninophilia with deposition of homogeneous amyloid masses, beginning in the perifollicular zone, other generations of cells gradually passing through the same phases until the greater part of the pulp was involved. Though during the early stages the deposits form more or less well-defined globular precipitates corresponding to the cellular origin (Fig. 6), the continued administration of cortisone caused a deposition of completely confluent masses without any remnants of cellular structure (Fig. 8). The deposits gave a positive reaction with Congo red, but only a few cases reacted with Eden's methyl violet stain, and none with toluidin blue or Hotchkiss periodic acid stain. After prolonged treatment with casein or casein followed by cortisone, there also appeared more or less pronounced deposits in the liver, the glomeruli of the kidneys, and the adrenal glands, indicating a weaker and later pyroninophilia of the mesenchymal derivative cells in these organs than that in the spleen.

The cortisone treatment caused a reduction of the adrenal glands, which had become hypertrophic after the preceding casein treatment.

Effect of Cortisone in Producing Amyloidosis in Rabbits

In a previous paper (Teilum and others, 1950), the findings in hyperimmunized rabbits after treatment with cortisone were described. Besides a marked regression of massive accumulations of plasma cells in the spleen in some cases a homogeneous substance appeared in the perifollicular zone in the spleen. Even if it failed to give characteristic staining reactions for amyloid, which is often the case in experimental amyloidosis, the localization and appearance were quite characteristic, and these cases certainly presented an amyloid alteration. Where this

change in the spleen had been ascertained by biopsy before administration of cortisone a marked increase of the depositions occurred afterwards.

With this may be compared the development of amyloid nephrosis in cortisone-treated rabbits with nephrotic syndrome (Teilum and others, 1951).

In mice treated in advance with repeated injections of casein, and in rabbits hyperimmunized for many months with killed Pfeiffer bacillus culture, cortisone has essentially the same effect: inhibition of pyroninophilic cells (including plasma cells), appearance of reticulosis where the cells display a pale, homogeneous, non-pyroninophilic substance, and—in certain cases—a prompt appearance of amyloid beginning in the perifollicular zone of the spleen.

Morphological Phases in Formation of Amyloid

The morphological studies at various stages of the amyloid synthesis in the spleen and of the influence of cortisone and ascorbic acid on this synthesis show that pronounced pyroninophilia of mesenchymal derivative cells in the spleen and other organs is fundamental to the pathogenesis of amyloidosis, depending in degree on the preceding pyroninophilia. As long as the amyloidosis developed after an antigen (casein injections or hyperimmunization) has not reached its maximum, pyroninophilic cells occur simultaneously around the amyloid masses already formed. In cases which do not later display any tendency to amyloid deposition, slight pyroninophilia is found in biopsy material from the spleen. The pyroninophilic reaction is usually most pronounced in the reticulum cells of the spleen, but may also be seen in other mesenchymal derivative cells in the liver, the glomeruli of the kidneys, and the interstitial tissue, corresponding, that is, to all the usual localizations of amyloid or hyaline.

As a series of examinations have shown it to be highly probable that the plasma cells are capable of producing antibodies (Bing and Plum, 1937; Bjørneboe and Gormsen, 1943; Fagraeus, 1948; and Ehrich and others, 1949), and the pyroninophilic mesenchymal cells occur in parallel with the accumulations of pyroninophilic plasma cells in the reticulo-endothelial system, there seems to be a close pathogenetic relation between antigenic influences and the development of hyaline or amyloid (Teilum, 1948a, b).

The cytological findings in the spleen conform with the results of examinations of the electrophoretic pattern made by Letterer (1949) and Bohle and others (1950) in mice during the development of experimental amyloidosis. Letterer thus found a higher γ-globulin increase in amyloidosis-affected mice than in non-affected mice after fifteen injections of nucleic acid. Bohle and others found that the γ-globulin values in the serum rise sharply after twelve to twenty injections, whereas after thirty injections they are lower than the normal values. Compared with the subjects that did not develop amyloidosis, the mice affected after twelve to twenty injections had unquestionably elevated γ-globulin values, whereas those who developed it after thirty injections had lower γ-globulin values than those who were unaffected.

Our biopsies of the spleen show that widespread amyloidosis may develop in mice a few days after the administration of cortisone.

Maintaining Effect of Ascorbic Acid on Pyroninophilic Cells in the Spleen in Hyperimmunized Rabbits

The interaction between ascorbic acid and cortisone and the occurrence of pyroninophilic cells in the spleen in hyperimmunized rabbits was examined in the following experiments. Eight rabbits, immunized with killed Pfeiffer bacillus culture for 6 to 12 months as previously described, were daily given varying doses of cortisone and ascorbic acid subcutaneously for 7 days, a few being treated with only one substance. Biopsy of the spleen was made on March 12, before treatment, and being treated for 7 days they were all killed on March 20. All the biopsies showed a moderate accumulation of plasma cells with incipient regression. Dosages of 5, 10, 15, and 20 mg. cortisone daily caused an almost complete regression of the plasma cells in the spleen in each case, in spite of the simultaneous administration of 333 mg. ascorbic acid daily by hypodermic injection, but whereas the control, which received neither ascorbic acid nor cortisone, also displayed some regression of the pyroninophilia 8 days after the biopsy, the rabbit which had received ascorbic acid without cortisone, presented a violent increase of pyroninophilic cells, which formed broad, proliferating zones perifollicularly and in the pulp (Fig. 7). This effect was later confirmed in a larger group of animals (Teilum and others, 1952).

Also, in experiments with casein-treated mice, which showed only a weak pyroninophilia at biopsy of the spleen, the pyroninophilia increased after 0·1 mg. ascorbic acid daily for 5 days, but this change did not appear in controls not treated with ascorbic acid.

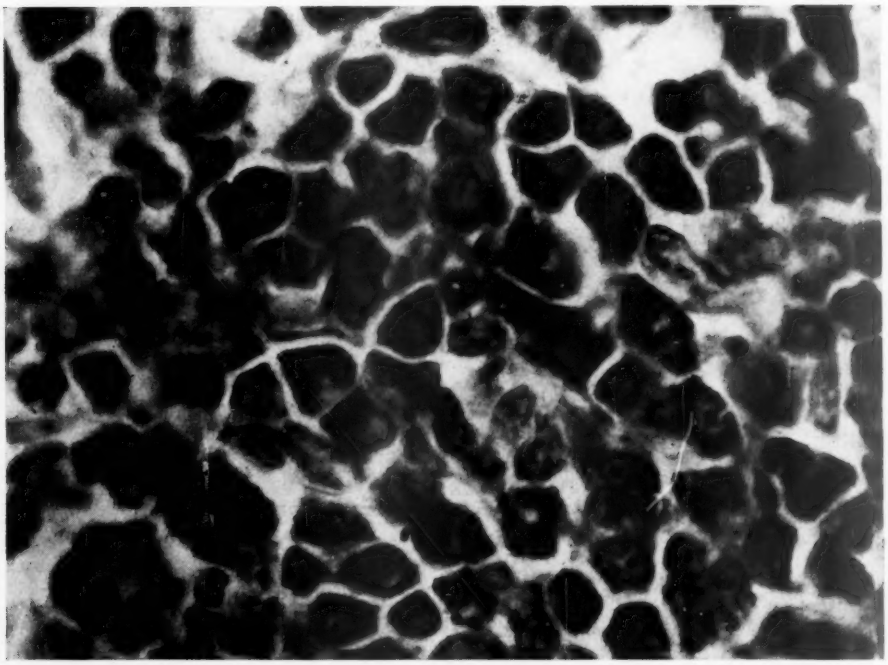

FIG. 7.—Re-appearance of plasma cells and pyroninophilic cells in spleen after administration of ascorbic acid. Hyperimmunized rabbit. Pyronin-methylgreen. ×950.

The action of ascorbic acid in causing amyloidosis in the spleen in casein-treated mice was shown in the following experiment:

Ten mice treated with injections of 0·5 ml. sodium caseinate for 5 days weekly from September 29 to November 6, showed very slight amyloid deposits in the spleen or none at all, whereas ten mice receiving 0·2 mg. ascorbic acid daily in addition showed a moderate amyloid deposition in the perifollicular zone.

This indicates that ascorbic acid activates the formation of pyroninophilic substance in mesenchymal cells and is thus of decisive importance in the production of globulins (and antibodies).

Casein- and cortisone-treated mice with a diffuse amyloidosis in the spleen at biopsy (Fig. 8), after a period of 4 weeks without any injections, showed a pronounced tendency for the amyloid changes to regress, so that they became more localized, with homogeneous depositions and masses characteristic of the early stages. After treatment with daily injections of 0·2 mg. ascorbic acid daily, the regression during this 4-week period was very pronounced (Fig. 9, overleaf).

Comment.—These results indicate that amyloidosis represents a dysfunctional phase in the activity of reticulo-endothelial and other mesenchymal cells, which display essentially the same alterations. An active *pyroninophilic* phase may be distinguished, corresponding to the active phase in such diseases of the mesenchymal tissue as rheumatic and pararheumatic conditions, sarcoidosis, and acute glomerulonephritis. This phase is characterized by:

(*i*) the occurrence of pyroninophilic mesenchymal cells, which we have been able to demonstrate in various organs, such as the spleen, kidneys, and liver,

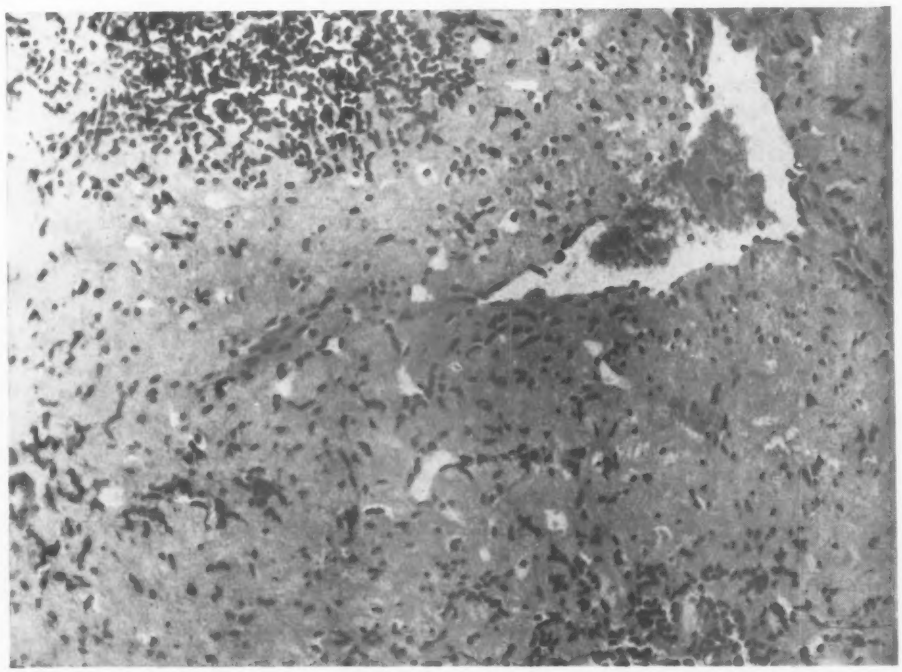

FIG. 8.—Biopsy of spleen in mouse treated with casein injections and further injections of cortisone showing diffuse amyloidosis (cf. Fig. 9, overleaf.) Haematoxylin and eosin. ×160.

(*ii*) the accumulation of plasma cells in the reticulo-endothelial system,
(*iii*) elevated serum γ-globulin values with increased production of antibodies,
(*iv*) the occurrence, in many cases, of metachromatic extracellular material.

Experimentally, all these morphological reactions have been accentuated after the administration of ascorbic acid. Further, it appears that all the changes characteristic of this phase are inhibited by the continued administration of cortisone in large doses. In certain cases this may produce hyalinosis, as, for instance, in the reticulum of the spleen (Teilum and others, 1950), and in cases of prolonged stress, for instance, in repeated stimulation of the immune mechanism, the cortisone treatment will result in the development of amyloidosis. This, then, may be distinguished as a negative phase, and is indicative of a perverted function of the mesenchymal cell with regard to the protein synthesis. Pirani and others (1949) succeeded in producing experimental amyloidosis in guinea-pigs fed on scorbutogenic diets for 8 weeks or longer. In addition to hyperplasia of the adrenal cortex, which must be considered an alarm reaction, Teilum and others (1952) found pyroninophilic cells in the spleen, which later underwent a transition to a pale, non-pyroninophilic, pre-amyloid reticulosis accompanied by changes in the electrophoretic pattern, showing the same morphological phase development as is seen in experimental amyloidosis caused by repeated stimulation of the immune mechanism and associated with similar changes in the adrenal cortex and serum globulins.

In amyloidosis produced in widely different ways the common denominator is thus seen to be a change in the protein synthesis of mesenchymal derivative

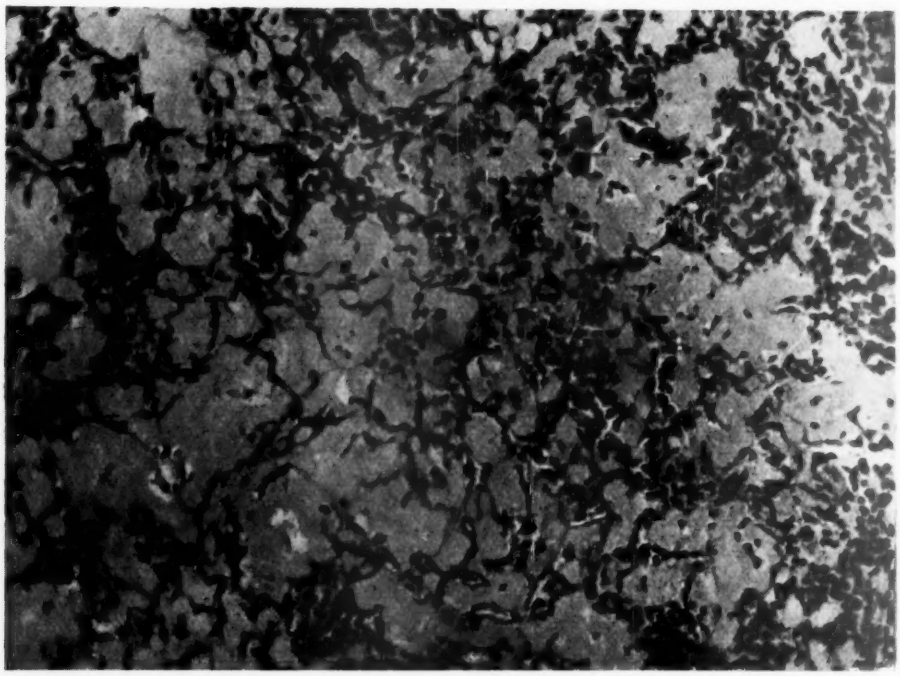

FIG. 9.—Regressive changes of amyloid in the spleen of same animal as Fig. 8 after further administration of ascorbic acid for 4 weeks. Haematoxylin and eosin. ×160.

cells controlled by an interaction between ascorbic acid and a hormone of the adrenal cortex similar to cortisone.

Special attention has been given to the possible role of ascorbic acid in adaptation and the development of the General Adaptation Syndrome (Selye, 1950). The importance of ascorbic acid in connection with the pituitary-adrenal-cortex mechanism is obvious from the high concentration in the adrenal cortex and the rapid fall of ascorbic acid in response to pituitary hormone (Pincus, 1947). Dugal and Thérien (1949) found that, when large doses of ascorbic acid were given to guinea-pigs, the enlargement of the adrenals on exposure to cold was prevented, although the animals were more resistant than the untreated controls. According to this theory, the proliferation of the cortex has been claimed not as a direct effect of corticotropin, but as a local response to the exhaustion of sources of energy due to corticotropin stimulation of hormone synthesis and release.

Antagonistic Effects of Cortisone and Ascorbic Acid on the Mesenchymal Tissue

Since the appearance of cortisone it has been possible to ascertain its effects on the reactions of the mesenchymal tissue. On closer consideration it appears that these effects are actually identical with those previously found in experimental ascorbic acid deficiency. In addition to the antagonistic effects of ascorbic acid and cortisone on experimental amyloidosis and pyroninophilia (ribonucleic acid synthesis) of mesenchymal cells here described, the following points may be mentioned (Table II). A reduced capacity for wound healing and a delayed development of granulation tissue after the administration of corticotropin or cortisone have been observed in numerous cases in animal and man. This inhibition of all connective tissue elements conforms with the histological studies of Wolbach (1933) on the influence of vitamin C deficiency on wound healing in guinea-pigs.

TABLE II
ANTAGONISTIC EFFECTS OF CORTISONE AND ASCORBIC ACID ON MESENCHYMAL TISSUE

Effect on Mesenchymal Tissue	Cortisone	Ascorbic Acid
Experimental Amyloidosis	+	−
Plasma Cells	−	+
Pyroninophilic Mesenchymal Cells (Ribonucleic acid synthesis)	−	+
Development of Granulation Tissue ..	−	+
Wound Healing	−	+
Production of Acid Mucopolysaccharides ..	−	+

Furthermore, in the course of ACTH or cortisone treatment of patients with rheumatoid arthritis, a decrease of the metachromatic elementary substance in the connective tissue of the skin has been demonstrated (Asboe-Hansen, 1950); conversely, Penney and Balfour (1949) found that in guinea-pigs on a diet without vitamin C ascorbic acid produces a rapid increase of mucopolysaccharides in experimental wound healing.

All these strikingly antagonistic effects on the mesenchymal tissue of cortisone and ascorbic acid are indicative of an interaction which is normally present between

these two substances, which together maintain the normal function and structure of the mesenchymal tissue. A few clinical observations may presumably be explained by such an interaction. For example, daily doses of 4 to 6 g. ascorbic acid without simultaneous administration of steroid hormone had a surprisingly favourable effect in certain cases of polyarthritis (Berg, 1950; Massell and others, 1950).

The examinations by Irons and others (1951) of ascorbic acid metabolism during ACTH and cortisone treatment of mesenchymal diseases also seem to indicate that the utilization of ascorbic acid is increased.

Fig. 10 illustrates the relationship between the functional and structural phases of reticulo-endothelial and other mesenchymal derivative cells and the apparently antagonistic effect of ascorbic acid-cortisone in the two dysfunctional stages (I. pyroninophilic (positive) and III. amyloid (negative)); hyalinosis, which represents II. an inactive phase of healing, corresponds to the axis of the abscissae. The apparent antagonism between ascorbic acid and cortisone supports the view that these two substances maintain the structure and function of the mesenchymal tissue *indirectly*. That the antagonism is not absolute, appears from several facts:

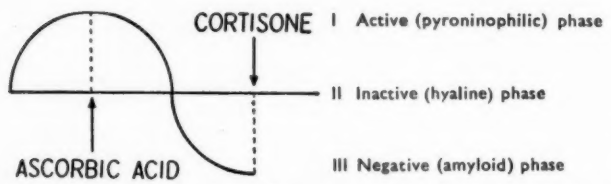

FIG. 10.—Diagram of cortisone-ascorbic acid interaction

both substances are necessary for the development of hyaline (phase of healing);
the effect of these substances on the mesenchyme seems to be dependent on the morphological phase of the mesenchymal cells *in loco* and to be related to Selye's " general adaptation syndrome ";
the changes of the mesenchymal cells pass through the same phases of development;
the degree of amyloid alteration in the negative phase seems to be determined not only by cortisone, but also by the degree of pyroninophilia in the preceding positive phase.

Probably most of the controversy regarding the effects of cortisone and ascorbic acid on the mesenchymal tissue may be explained by some such reciprocal mechanism of action.

As regards the development of amyloidosis, the effects of cortisone and ascorbic acid depend on the *condition of the tissues*, a fact that appears from the experiments. In an animal with pre-amyloid changes in an organ these will increase after treatment with cortisone, whereas other organs without such lesions may escape. The effect of cortisone on the mesenchymal tissue thus seems to depend on the local requirements for ascorbic acid and the possibilities of its utilization.

Mechanism of Development of Amyloidosis in Natural Disease

The experimental results may explain all types of amyloidosis in the natural diseases mentioned above, as it is evident that the conditions for amyloid-formation are present in all diseases where the regression of normal occurrence, or the development of hyalinosis (inactive phase) after the preceding pyroninophilia (active phase), fails to appear. The amyloid phase may thus be considered a perverted

phase in the cellular synthesis of protein, in which the interaction between ascorbic acid and a hormone of the adrenal cortex similar to cortisone is decisive. All forms of typical (secondary) amyloidosis are analogous with the experimental amyloidosis after prolonged immunization or protein therapy, whereas the atypical (primary) amyloidosis may be explained by an imbalance in the reciprocal effects of the two substances. The different localization in primary amyloidosis is the same as that of hyalinosis in generalized sclerodermia (myocardium, tongue; and striated musculature), and transitional forms between sclerodermia and primary amyloidosis are also known (Jørgensen, 1944). Stoeber (1934) described cases of allergic conditions combined with so-called genuine amyloidosis, and Cazal (1942) mentioned a case of amyloidosis in a 7-year-old girl with *un état d'anaphylactique* as the only aetiologic factor.

The amyloidosis of rheumatoid disease differs from the usual secondary amyloidosis (in chronic suppurative conditions) in that it represents in itself an abnormal phase occurring under certain special conditions in the morphogenesis of the disease process. Actually there will be a difference only of degree between " amyloidosis in rheumatoid arthritis " and " primary so-called atypical amyloidosis " in which the abnormal phase of mesenchymal disorder has very recently developed.

Role of Mucopolysaccharide in Formation of Amyloid

Disturbances in the protein synthesis in mesenchymal cells are important in the formation of amyloid, but there may be other contributory factors. The amyloid substance is now generally considered to be a glycoprotein in which a mucopolysaccharide is attached to a globulin. The discovery of the hyaluronidase group of enzymes has renewed interest in the chemistry of glycoproteins—mucins, chondroproteins (Wright, 1950).

Disturbance in the extracellular matrix is of first importance in mesenchymal disorder. Hamilton and Syverton (1950), examining the spread of metachromasia in the myocardium of patients who had died of rheumatic fever, found a striking conformity with the occurrence of mast cells and concluded that the degranulation of tissue mast cells with the liberation of an acid-reacting mucopolysaccharide plays a part in the focal rheumatic process. The relation between mast cells and mucopolysaccharides has recently been studied in detail (Asboe-Hansen, 1950). Corticotropin and cortisone as well as ascorbic acid influence the occurrence of the metachromatic elementary substance; Schmith and Faber (1949) also found the hyaluronidase-inhibitory effect of serum diminished during treatment of rheumatoid arthritis with ACTH.

Since metachromasia of the extracellular matrix (and in certain cases granulated mesenchymal cells of the mast cell type) is a characteristic component in the active phase of mesenchymal disorder, and, like pyroninophilia, is controlled by the adrenal cortex-ascorbic acid interaction, it may be that a mucopolysaccharide or a modified product is attached to the proteins during the depression of the positive phase. It has been shown that the carbohydrate ester, chondroitin sulphuric acid, is capable of uniting firmly with several proteins to form stoechiometrically well-defined compounds (Meyer and others, 1937).

The study of pyroninophilic mesenchymal cells as precursors of hyalinosis and amyloidosis shows the significance of changes of *cellular* function and structure in mesenchymal disease as well as disturbance of the extracellular matrix.

Summary

(1) The mechanism by which cortisone maintains the structure and function of mesenchymal tissue is an *indirect* one, mediated by ascorbic acid.

(2) Several functional and structural changes of reticulo-endothelial and other mesenchymal derivative cells, including *amyloidosis*, are shown to be controlled by the *interaction* of cortisone-ascorbic acid.

(3) In mice, previously treated for several weeks with injections of casein, insufficient to produce amyloidosis, a few injections of cortisone promptly resulted in the appearance of amyloid in the spleen.

(4) The occurrence of *pyroninophilic mesenchymal cells* is considered to be a fundamental precursor in the pathogenesis of amyloidosis or hyalinosis.

(5) In experimental mesenchymal disorder, as well as in the natural diseases, three *typical phases* can be established:

(*a*) *An active (positive) phase of pyroninophilia*, characterized by pyroninophilic mesenchymal cells in various organs and tissues, accumulation of plasma cells in the reticulo-endothelial system, elevated γ-globulin values in the serum, and, in many cases, metachromatic extra-cellular material.

(*b*) *An inactive healing phase of hyalinosis.*

(*c*) *A perverted (negative) phase of pre-amyloidosis or amyloidosis.*

Phase (*a*) is maintained by ascorbic acid and inhibited by cortisone; the continued administration of cortisone (with increased ascorbic acid deficit) may result in amyloidosis.

The established antagonistic effects of cortisone and ascorbic acid on mesenchymal tissue can be explained as an interaction of ascorbic acid and a hormone of the adrenal cortex of cortisone type controlling the phasic development in mesenchymal disorder.

(6) Thus the amyloid phase in rheumatoid arthritis and other conditions can be considered as a perverted phase in cellular synthesis of protein associated with a disturbance of some enzyme system.

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Action réciproque de la cortisone et de l'acide ascorbique dans la pathogénie de l'amyloïdose

RÉSUMÉ

(1) Le mécanisme par lequel lacortisone, hormone de l'écorce surrénale, maintient la structure et la fonction du tissu mésenchymateux, est *indirect*, par l'intermédiaire de l'acide ascorbique.

(2) On montre que plusieurs altérations fonctionnelles et structurelles des cellules réticulo-endothéliales et d'autres cellules d'origine mésenchymateuse, comme celles qu'on rencontre dans l'*amyloïdose*, sont contrôlées par *l'action réciproque de la cortisone et de l'acide ascorbique*.

(3) Chez des souris traitées préalablement pendant plusieurs semaines par des injections de caséine, insuffisantes pour produire l'amyloïdose, celle-ci apparut rapidement dans la rate après quelques injections de cortisone.

(4) On considère que la présence de *cellules mésenchymateuses pyroninophiles* est un élément précurseur fondamental dans la pathogénie de l'amyloïdose ou de la hyalinose.

(5) Dans les troubles mésenchymateux expérimentaux ainsi que cliniques, on peut distinguer trois phases:

(*a*) *Une phase pyroninophile active* (*positive*), caractérisée par des cellules mésenchymateuses pyroninophiles dans de divers organes et tissus, par l'accumulation des cellules plasmatiques dans le système réticulo-endothélial, par le taux élevé de la γ-globuline dans le sêrum et, dans beaucoop de cas, par la presence du matériel extra-cellulaire métachromatique.

(*b*) *Une phase inactive de réparation* (*hyalinose*).

(*c*) *Une phase pervertie* (*négative*), *pré-amyloïde ou amyloïde*.

La phase pyroninophile est maintenue par l'acide ascorbique et inhibée par la cortisone; l'administration continue de la cortisone—tandis que la pénurie d'acide ascorbique augmente—mène à l'amyloïdose.

L'effet antagoniste, bien prouvé, de la cortisone et de l'acide ascorbique sur les tissus mésenchymateux peut s'expliquer par l'action réciproque de l'acide ascorbique et d'une hormone de l'écorce surrénale du genre cortisone, contrôlant le développement phasique de trouble mésenchymateux.

(6) On peut donc considérer la phase amyloïde au cours de l'arthrite rhumatismale et des autres affections comme une phase pervertie de la synthèse cellulaire de la protéine, associée à un trouble de quelque système d'enzymes.

Acción recíproca de la cortisona y del ácido ascórbico en la patogenia de la amiloidosis

SUMARIO

(1) El mecanismo por el cual la cortisona, hormona de la corteza suprarrenal, mantiene la estructura y la función del tejido mesenquimatoso es *indirecto*, mediante el ácido ascórbico.

(2) Se demuestra que varias alteraciones funcionales y estructurales de las células réticulo-endoteliales y de otras células de origen mesenquimatoso, como las que se encuentranen *amiloidosis*, están controladas por la *acción recíproca de la cortisona y del ácido ascórbico*.

(3) En ratones, previamente tratados durante varias semanas por nyecciones de caseina, insuficientes para producir amiloidosis, ésta apareció rapidamente en el bazo después de pocas inyecciones de cortisona.

(4) Se considera que la presencia de las *células mesenquimatosas pironinófilas* es precursora fundamental en la patogenia de la amiloidosis y de la hialinosis.

(5) En disturbios mesenquimatosos experimentales así como en las enfermedades naturales se puede determinar tres *fases típicas*:

(*a*) *Fase pironinófila activa* (*positiva*), caracterizada por células mesenquimatosas pironinófilas en varios órganos y tejidos, por una acumulación de las células plasmáticas en el sistema retículo-endotelial, por la cifra aumentada de la gama-globulina en el suero y, en muchos casos, por la presencia de material extra-celular metacromático.

(*b*) *Fase inactiva de reparo* (*hialinosis*).

(*c*) *Fase pre-amiloide o amiloide, pervertida* (*negativa*).

El ácido ascorbico mantiene la fase pironinófila y la cortisona la inhibe; la administración continua de cortisona—mientras crezca el déficit del ácido ascorbicó—motiva una amiloidosis.

Los efectos antagónicos comprobados de la cortisona y del ácido ascórbico sobre el tejido mesenquimatoso pueden explicarse por la acción recíproca del ácido ascórbico y de una hormona de la corteza suprarrenal de tipo cortisona, controlando el desarrollo fásico del disturbio mesenquimatoso.

(6) Así pues, la fase amiloide en la artritis reumatoide y en otras afecciones puede considerarse como una fase pervertida de la síntesis celular de la proteina, asociada con un disturbio de algún sistema de enzimas.

INTERPRETATION OF MULTIPLE BIOPSIES OF SYNOVIAL TISSUE IN RHEUMATIC DISEASES*

BY

B. CRUICKSHANK

From the Department of Pathology and the Rheumatic Research Unit, University of Edinburgh

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The alternating clinical activity and remission which characterize such chronic rheumatic diseases as rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, and gout are reflected in the histopathology of the synovial tissue. Recurrent phases of inflammation and healing produce a complex picture in all except very early cases. It is no new observation that histological examination, by itself, gives no indication of the duration of the disease. Previous workers have also mentioned the fact that different parts of the same joint show varying appearances (Allison and Ghormley, 1931; Parker and Keefer, 1935; Ghormley, 1938; Jordan, 1938; Rosenberg, 1949), but have laid little stress on this feature.

The introduction of cortisone and ACTH to clinical medicine and the production of a punch biopsy instrument for use in joints (Polley and Bickel, 1951) have stimulated interest in the histopathology of synovial tissue in the chronic rheumatic diseases. The use of the hormones raises the question whether or not the clinical improvement induced by them is associated with changes in the tissues. The use of the punch biopsy instrument has provided the clinician and the pathologist with a ready means of obtaining synovial tissue from joints. Several reports have already appeared in which it is claimed that synovial tissue taken during, or after, the administration of cortisone or ACTH in rheumatoid arthritis shows changes attributable to these hormones. Although the authors of some of these reports are cautious about the interpretation of the histological appearances (Giansiracusa and others, 1951), others accept decrease in the amount of inflammation, oedema, necrosis, or surface hyperplasia as due to the hormones (Hench and others, 1950).

The purpose of this study is to demonstrate the variations in the histopathology of synovial tissue taken at the same time from different parts of joints in these diseases. Particular attention has been paid to features which might be interpreted as an effect of treatment with drugs.

Material

Synovial tissue was obtained at autopsy or open operation from 35 joints in cases of rheumatoid arthritis, consisting of three shoulders, three elbows, the proximal interphalangeal joint of one finger, and 28 knees. Blocks were taken from the suprapatellar pouch, the medial or lateral compartment, and the infrapatellar fat pad of each knee, and, in nine cases, two adjacent blocks were taken from one or other of these regions. An average of three blocks was taken from different parts of the other joints.

Multiple blocks were also taken from one sternoclavicular joint, four hips, and one

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knee in ankylosing spondylitis; from one elbow and nine knees in rheumatic fever; from four knees in systemic lupus erythematosus; from one knee in gout; and from four knees in polyarteritis nodosa.

All blocks were embedded in paraffin and routine haematoxylin and eosin sections were studied. Comparison of the appearances in different sections in rheumatoid arthritis was made by observing the occurrence of the features regarded by Collins (1949) as characteristic of that condition. The presence or absence of necrosis and the degree of fibrosis were also noted. The same criteria were applied in ankylosing spondylitis, for the lesions in that condition are similar to those of rheumatoid arthritis (Cruickshank, 1951). In the other diseases, the occurrence and degree of proliferation, inflammation, necrosis, and fibrosis were noted. In assessing variations in the histological appearances in these diseases, due consideration was given to the normal variations in histology in synovial tissue in different parts of the joints (Key, 1932).

Results

Rheumatoid Arthritis.—In sixteen of the joints, the various sections showed the same features, or differed only in minor points, such as variations in the degree and extent of surface hyperplasia or the degree of oedema and congestion. Nine joints showed more noticeable variations, such as the presence of necrosis in only one section, the presence of diffuse granulation tissue alternating with the more typical appearances or variations in the number and distribution of lymphocytes and plasma cells.

In ten of the joints, there were major variations in the histological appearances.

FIG. 1.—Synovial tissue from right knee. Male, aged 49. Rheumatoid arthritis affected the knee for 11 years; no drug treatment. One of many villi, showing hyperplasia of surface cells, oedema, congestion, and massive infiltration with round cells, including large foci. (×100.)

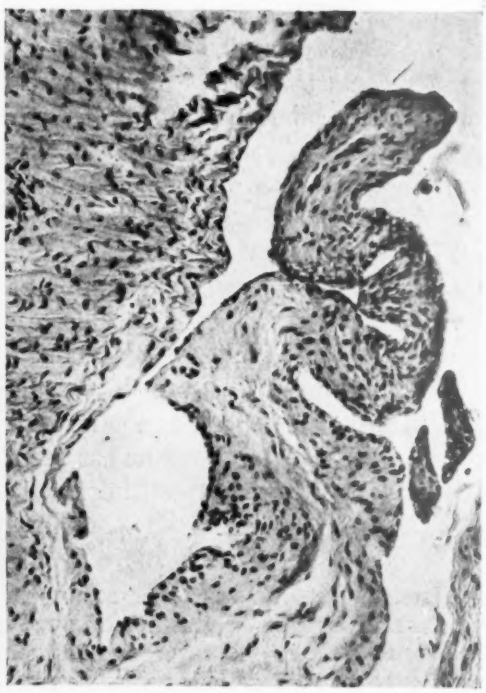

FIG. 2.—Same case as Fig. 1. Section from adjacent block, showing marked fibrosis. (×100.)

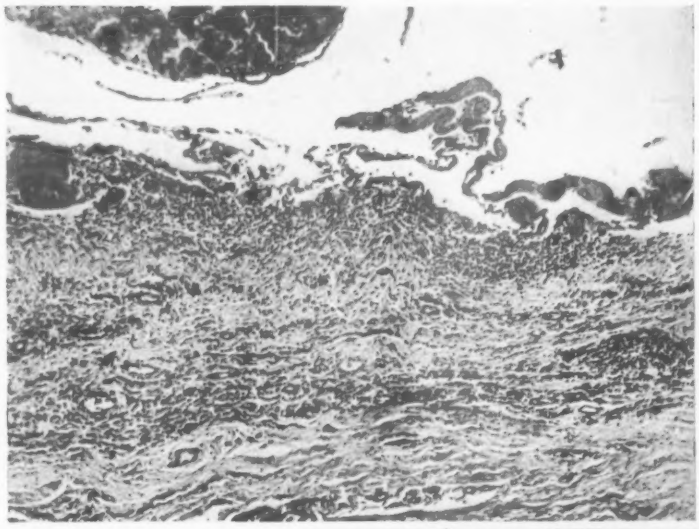

FIG. 3.—Synovial tissue from right knee. Female, aged 75. Rheumatoid arthritis had affected the knee for 2 years; no drug treatment. Extensive necrosis (top), diffuse round-cell infiltration, congestion, and some fibrosis. (×50.)

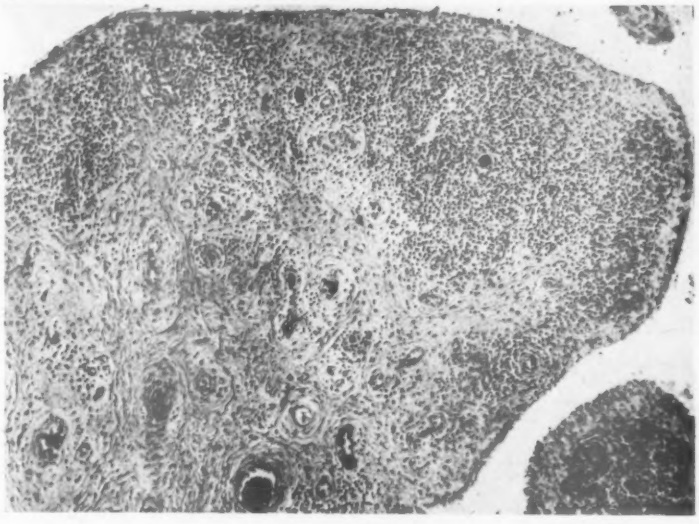

FIG. 4.—Same case as Fig. 3. Large villous, showing fine fibrosis superimposed upon diffuse round-cell infiltration. (×50.)

For example, in one knee, one section showed marked hyperplasia and intense inflammation (Fig. 1), whereas these features were absent in another section, which showed well-marked fibrosis (Fig. 2). In another knee, fibrosis was predominant in one section, slight in another, and absent from a third. Three sections from an elbow showed, respectively, marked inflammation without fibrosis, slight inflammation without fibrosis, and marked fibrosis without inflammation. Variations in the relative degrees of inflammation and fibrosis, which might be interpreted as indicative, respectively, of activity and healing, were seen in eight joints (Figs 1-4). Such variations were seen not only in blocks from different regions of a joint, but also sometimes in adjacent blocks from the same region of a joint, and occasionally in a single section.

The cases of rheumatoid arthritis were analysed to see if the histological appearances could be correlated with the duration, stage (Steinbrocker and others, 1949), or clinical activity of the disease in the affected joint, or with drug therapy. The number of cases studied was too small to permit statistical analysis, but certain

TABLE I
RELATIONSHIP BETWEEN CLINICAL ACTIVITY OF JOINTS IN RHEUMATOID ARTHRITIS AND VARIATIONS IN THE HISTOPATHOLOGICAL APPEARANCES OF SYNOVIAL TISSUE

Degree of Variation in Histology	Total	Clinically Active	
		No.	Per cent.
Minor	12	5	42
Moderate	9	7	78
Major	9	8	89
Total	30	20	67

trends were noted. Thus, a much higher proportion of those joints in which major differences were seen were clinically active than of those in which only minor differences were present (Table I). Similarly, nearly three-quarters of the cases showing major differences were of two years' duration or less, whereas more than three-quarters of those showing minor differences were of more than two years' duration. The relationship between the histological changes and the stage of the disease showed the same trend. All the cases with major differences were at Stages I or II, whereas three-quarters of those with minor differences were at Stages III or IV. No relationship was noted between the administration of gold or other drugs (excluding analgesics) and the degree of variation (Table II).

TABLE II
RELATIONSHIP BETWEEN ADMINISTRATION OF GOLD AND OTHER DRUGS IN RHEUMATOID ARTHRITIS AND VARIATIONS IN THE HISTOPATHOLOGICAL APPEARANCES OF SYNOVIAL TISSUE

Degree of Variation in Histology	Total	No Gold Given	
		No.	Per cent.
Minor	13	5	38
Moderate	9	4	44
Major	8	2	25
Total	30	11	37

Ankylosing Spondylitis.—The variations in appearance seen here were of minor degree only. This may be due to the fact that a substantial degree of inflammation was seen in only two joints.

Rheumatic Fever.—The appearances in two of these joints were normal. In another four, the lesions were mild, consisting of congestion, slight hyperplasia of the synovial cells, minimal round-cell infiltration, and occasional patches of necrosis of the surface. More marked changes, including patches of necrosis in the deeper tissues or slight villous hyperplasia with both round-cell and histiocyte response, were seen in four joints. In only one of these cases had there been a previous attack of rheumatic fever. Two knees showed appearances in different sections, varying from patchy necrosis in one, congestion and slight round-cell infiltration in a second,

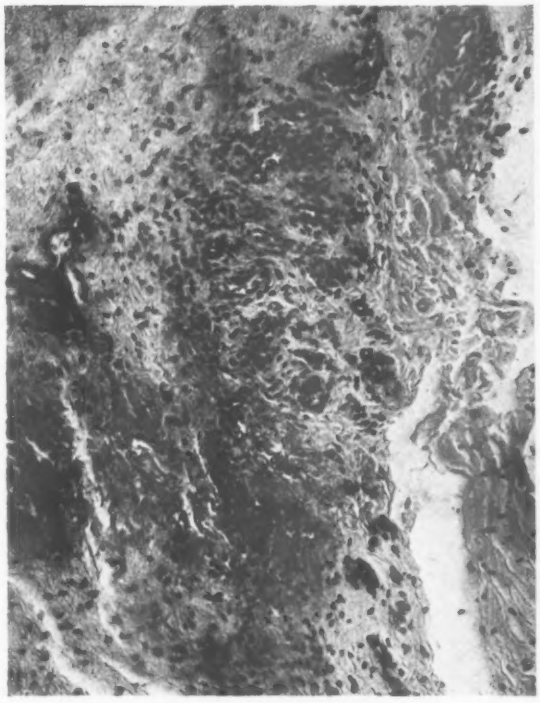

FIG. 5.—Synovial tissue from left elbow. Male, aged 49. Rheumatic fever of 10 days' duration; previous attack 10 years ago. Large area of necrosis (right), with round-cell response and congestion. (×100.)

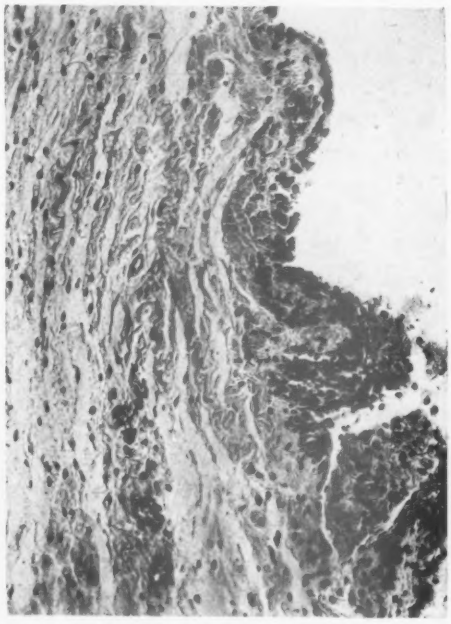

FIG. 6.—Same case as Fig. 5. Slight proliferation of surface cells, congestion, oedema, and minimal lymphocytic infiltration. (×100.)

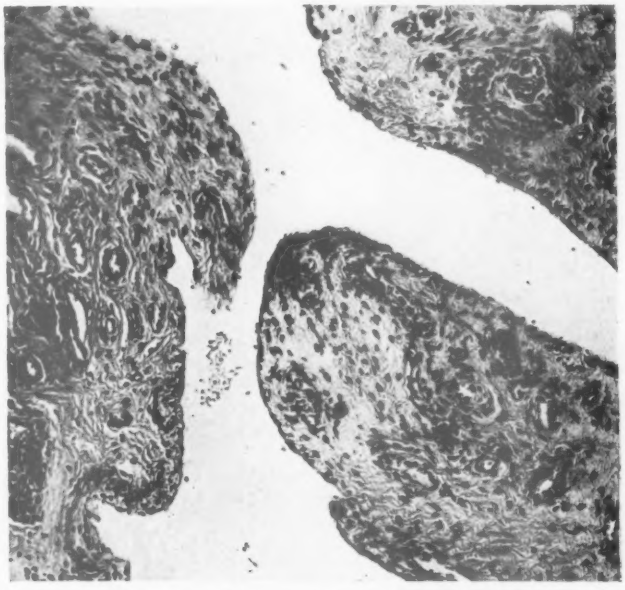

FIG. 7.—Same case as Figs 5 and 6. Villous hyperplasia and fibrosis, with congestion and slight lymphocytic infiltration. (×100.)

to fibrosis in a third (Figs 5-7)

Systemic Lupus Erythematosus.—A wide range of appearances was seen, the mildest lesion resembling that seen in rheumatic fever, whereas in more marked cases there was villous hyperplasia, slight hyperplasia of the surface cells, and more pronounced round-cell infiltration. Minor variations were seen in one joint and marked variations in another. In the latter, one section showed patchy surface necrosis with oedema and slight round-cell infiltration, a second showed acute necrotizing arteritis with marked acute inflammation of the adjacent tissue, and a

third showed fibrosis (Figs 8-10). These variations were not related to therapy.

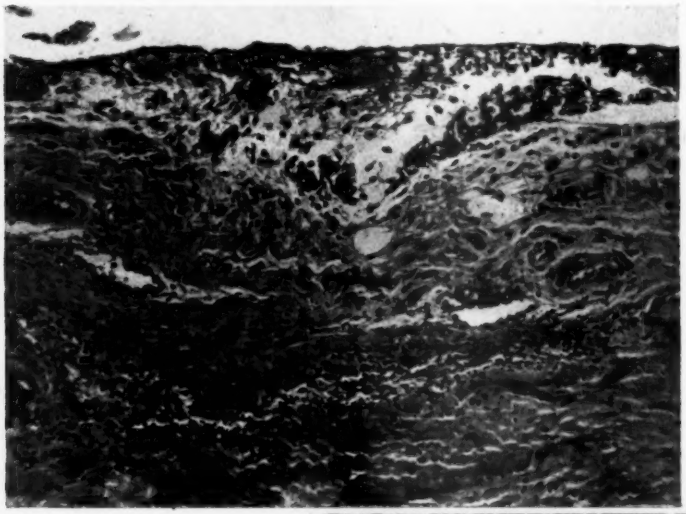

FIG. 8.—Synovial tissue from left knee. Female, aged 45. Systemic lupus erythematosus had affected the knee for 3 months. No response to salicylates; no gold. Necrosis and oedema of surface (top), slight round-cell infiltration below. (× 100.)

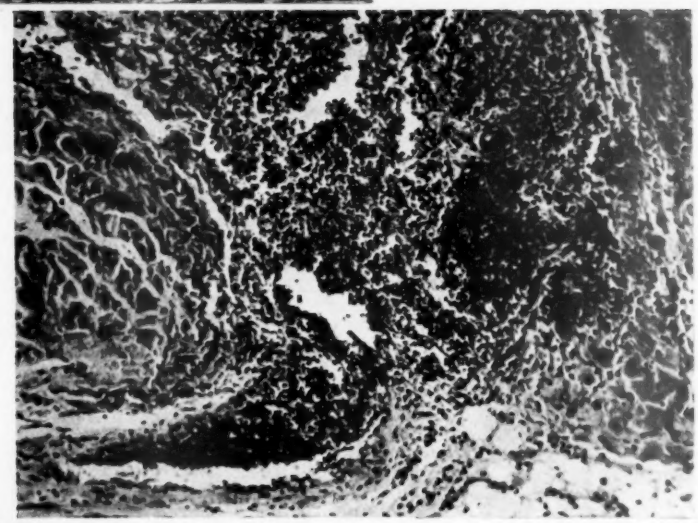

FIG. 9.—Same case as Fig. 8. Necrotizing arteritis (bottom, left) and marked acute inflammation of adjacent tissue. (× 100.)

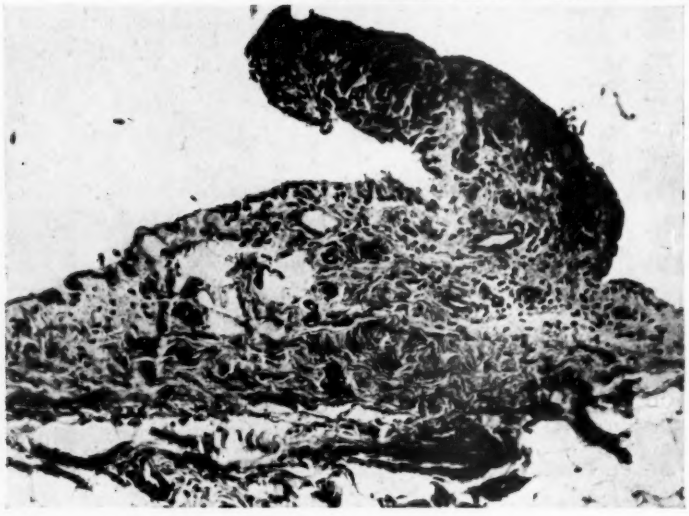

FIG. 10.—Same case as Figs 8 and 9. Fibrosis and slight lymphocytic infiltration of a small villous. (× 100.)

Gout.—Two sections from the knee of a case of gout showed striking differences, inflammation being predominant in one and fibrosis in the other (Figs 11 and 12).

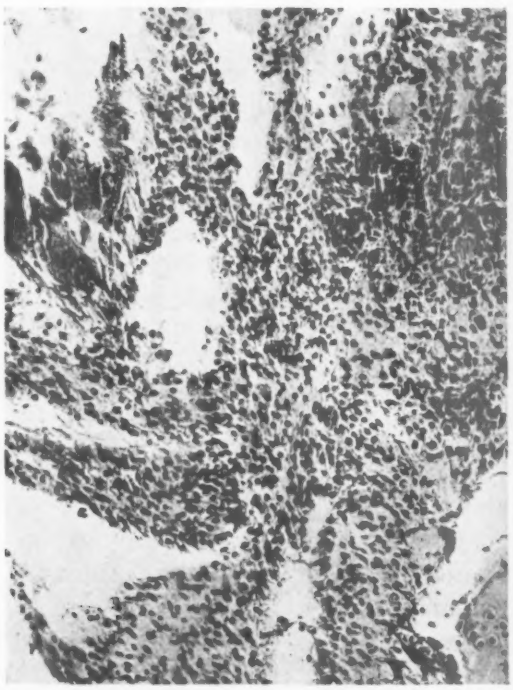

FIG. 11.—Synovial tissue from left knee. Male, aged 65. Gout of 38 years' duration. Small urate deposits (top, right), marked diffuse round-cell infiltration and hyperplasia of synovial tissue. (×100.)

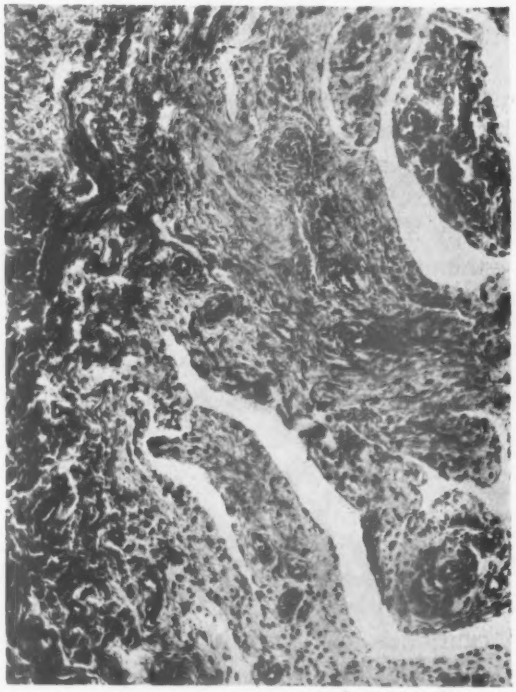

FIG. 12.—Same case as Fig. 11. Villous hyperplasia with fibrosis. (×75.)

Polyarteritis Nodosa.—The synovial tissue in two of the joints was normal. In the other two, which were from one patient, occasional arteries and veins showed healed lesions. Slight fibrosis and thrombosis of many capillaries was also seen, but there was no evidence of acute lesions.

Discussion

This study shows that marked variations in the histopathological appearances in synovial tissue taken from different parts of a joint are not uncommon in rheumatoid arthritis. Minor variations, affecting particularly the relative amounts of inflammation and fibrosis, are frequently seen in this disease. Major differences occur more often than minor ones in cases which are of short duration, clinically active, or at an early stage of the disease, whereas minor variations are more frequent in cases of longer duration, clinically inactive, or at a later stage. The degree of variation in the histopathology is not related to the administration of gold, for in over one-third of those cases where moderate or marked differences occurred, no gold had been given.

Although only slight variations have been noted here in the appearances of sections from joints in ankylosing spondylitis, the close parallel between the

lesions and the clinical course in that condition and in rheumatoid arthritis suggests that similar variations in histology might be expected to occur in spondylitis.

The lesions which occur in the synovial tissues in most cases of rheumatic fever and systemic lupus erythematosus are such that striking differences in the appearance in different parts of a joint are much less likely to occur than in rheumatoid arthritis. Indeed, Klinge (1930) stressed that extensive search of many blocks of synovial tissue may be necessary in order to make a definite diagnosis of rheumatic fever. Nevertheless, this study has shown that, in both diseases, parts of the synovial tissue may show fine fibrosis, whereas in other parts recent necrosis and inflammation may be seen. In neither disease could the appearances be correlated with drug therapy. The synovial lesions in polyarteritis nodosa show the same patchy distribution as appears elsewhere in the body in this disease. Furthermore, it is to be expected that vessels in the synovial tissue, like those in other tissues, may show all stages of the disease, from acute necrotizing arteritis to completely healed lesions, even in unhealed cases.

In this investigation all the changes in synovial tissue reported in cases of rheumatoid arthritis receiving cortisone or ACTH, have been seen to occur naturally in the course of the disease. Although the administration of these drugs may produce a dramatic clinical response, much caution must be exercised in attributing to them, or to any other drugs which may be introduced in the future, changes which may, in fact, occur in the natural course of the disease. The same caution is necessary in other diseases which respond to the same drugs, such as systemic lupus erythematosus, rheumatic fever, gout, and ankylosing spondylitis.

Summary

(1) Multiple blocks have been taken at one time from different parts of sixty joints, 35 being affected by rheumatoid arthritis, six by ankylosing spondylitis, ten by rheumatic fever, four by systemic lupus erythematosus, one by gout, and four by polyarteritis nodosa.

(2) Major variations were seen in the histopathological appearances in different regions of ten of the joints from rheumatoid arthritis. Variations in the relative degrees of inflammation and fibrosis, which might be interpreted as indicative of activity and healing respectively, were seen in eight joints. Similar variations were also seen in adjacent blocks taken from the same region of one joint and sometimes in a single section.

(3) Minor variations in degrees of inflammation and fibrosis were seen in two joints in rheumatic fever, two in systemic lupus erythematosus, and one in gout.

(4) These variations were not related to treatment, but had occurred naturally in the course of the diseases. Similar changes in rheumatoid arthritis have been attributed by some authors to the action of cortisone and ACTH, but caution should be exercised in attributing to drugs changes which are known to occur naturally in the synovial tissue in the course of rheumatic diseases.

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Interprétation des prélèvements multiples du tissu sinovial dans l'arthrite rhumatismale

RÉSUMÉ

(1) Des tranches multiples furent prélevées à un moment donné sur de différentes parties de 60 articulations, dont 35 atteintes d'arthrite rhumatismale, 6 de spondylite ankylosante, 10 de rhumatismale, articulaire aigu, 4 de lupus érythémateux disséminé, une de goutte, et 4 de polyartérite noueuse.

(2) Des variations majeures furent observées dix fois dans l'apparence histo-pathologique de différentes régions de la même articulation des cas d'arthrite rhumatismale. Des variations concernant l'intensité relative d'inflammation et de fibrose, pouvant être interprétées respectivement comme signes d'activité ou de guérison, furent observées dans huit articulations. On vit aussi des variations similaires dans les tranches adjacentes prélevées sur la même partie d'une articulation et quelquefois dans la même coupe.

(3) Des variations de moindre importance concernant l'intensité d'inflammation et de fibrose furent notées dans deux articulations des cas de rhumatisme articulaire aigu, deux fois dans le lupus érythémateux disséminé, et une fois dans la goutte.

(4) Ces variations n'étaient pas liées au traitement mais s'étaient présentées spontanément au cours des maladies. Certains auteurs avaient attribué des altérations similaires dans l'arthrite rhumatismale à l'action de la cortisone et de l'ACTH; il est donc nécessaire d'être prudent lorsqu'on attribue aux médicaments des modifications susceptibles de se produire naturellement dans le tissu synovial au cours des affections rhumatismales.

La interpretación de biopsias multiples del tejido sinovial en la artritis reumatoide

SUMARIO

(1) Biopsias multiples fueron hechas en un momento determinado en partes diferentes de 60 articulaciones, 35 de ellas de casos de artritis reumatoide, 6 de espondilitis anquilosante, 10 de reumatismo poliarticular agudo, 4 de lupus eritematoso diseminado, una de gota, y 4 de poliarteritis nodosa.

(2) Variaciones de mayor importancia fueron observadas diez veces en la apariencia histopatológica de diferentes regiones de la misma articulación en casos de artritis reumatoide. Variaciones de la intensidad relativa de inflamación y de fibrosis, expuestas a la interpretación de actividad o de cura según el caso, fueron vistas en ocho articulaciones. Viéronse también variaciones semejantes en fragmentos adyacentes recogidos en la misma parte de una articulación y, a veces, en el mismo corte.

(3) Variaciones de menor importancia respecto a la intensidad de inflamación y de fibrosis en la misma articulación, fueron observadas dos veces en el reumatismo poliarticular agudo, dos veces en el lupus eritematoso diseminado y una vez en la gota.

(4) Estas variaciones no se relacionaban con el tratamiento sino ocurrían naturalmente en el curso de la enfermedad. Alteraciones similares en la artritis reumatoide habían sido atribuidos por algunos autores a la acción de la cortisona y de la ACTH; hay, pues, que tener cuidado, cuando se atribuye a medicamentos las alteraciones que se sabe capaces de ocurrir en el curso natural de las enfermedades reumáticas.

JOINT AND NEUROMUSCULAR MANIFESTATIONS OF PERIARTERITIS NODOSA

BY

EDWARD W. LOWMAN

New York City, N.Y.

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Periarteritis nodosa is a protean disease which may manifest itself in multiple systems of the body. Muscle soreness and arthralgias are common early components of the disease complex, but indications are that frank joint reactions are infrequent and arthritis rare.

In an effort to clarify the status of joint and of neuromuscular manifestations in periarteritis, the records of 43 patients who died of the disease have been reviewed. In each case the diagnosis was proven by *post-mortem* examination, and in one changes in the synovial tissue were studied histologically.

Periarteritis nodosa is a pan-vasculitis (Dunbar, 1936; Spiegel, 1936) producing greatest damage on the arterial side of the circulatory system. It involves arteries, arterioles, capillaries, and veins, the greatest damage occurring in the smaller arteries and arterioles. The initial phase is one of acute damage with oedema and necrosis; this usually affects the media first, and then spreads to the other coats and beyond to contiguous perivascular tissue. This acute phase of damage and destruction is followed by a reparative or granulation stage which finally heals by fibrosis. As a result of the inflammatory process compromising the calibre of the blood vessels, tissue distal to and normally dependent upon them for nourishment suffers from ischaemia. The degree of ischaemia depends upon the degree of vascular embarrassment and the availability of collateral circulation; it may vary from transient ischaemia to frank infarction. The involved vessel may develop thrombosis, aneurysm, or a rupture resulting in local haemorrhage (Diaz-Rivera and Miller, 1946).

Any organ of the body may be involved; these are, in order of frequency, kidneys, heart, liver, gastro-intestinal tract, mesenteric arteries, muscles, spleen, lungs, and peripheral and central nervous system. Curtis and Coffey (1934) classified the disease into six types occurring singly or in combination: gastro-intestinal, renal, neuro-muscular, cardiac, cerebral, and cutaneous.

The aetiology of the disease is not established. Many investigators, including Spiegel (1936), Boyd (1938), and Friedberg and Gross (1934), have noted the high incidence of rheumatic fever in patients developing periarteritis nodosa and have considered this significant. The experimental work of Rich (1942) and of Rich and Gregory (1943) in producing lesions in rabbits resembling those of periarteritis nodosa by hypersensitivity reaction with horse serum stimulated much interest in the allergic potentialities in the aetiology of this disease. It is felt by many (Spiegel, 1936; Cohen and others, 1936; Keefer, 1943) that it is of allergic

origin and that the vascular lesions result from a severe allergic reaction, giving rise to damage to the responding vascular system. Cohen and others (1936) think that anyone suffering from an allergy is a potential victim of periarteritis nodosa.

Neuromuscular and joint symptoms are common early manifestations of periarteritis nodosa. The neuromuscular changes are consequent upon the localization of the destructive vascular lesions in vessels supplying the muscles or the nerves of the muscles. Ischaemia resulting from the arterial embarrassment produces either a myositis with localized tenderness or a neuritis of the mono- or polyneuritis type. These may be minimal or may be present as the predominant features of the disease. Objectively, there may be tenderness along one or more peripheral nerves, or there may be only localized areas of muscle tenderness with or without palpable tender nodules. Typically the tenderness is aggravated by activity or by palpation and improves with rest. Weakness may be a subjective manifestation of aesthenia or, in the case of peripheral neuritis, may represent a true motor nerve impairment and any degree of paralysis may develop.

TABLE I

JOINT INVOLVEMENT IN PERIARTERITIS NODOSA

Author	Date	Total Patients	Patients reporting Prodromal Joint Symptoms			
			One Joint		More than One Joint	
			No.	%	No.	%
Boyd	1938	100	27	27		
Spiegel	1936	17	5	29		
Jones	1942	14			9	64
Diaz-Rivera and Miller	1946	7			1	14
Harris, Lynch and O'Hare	1939	6			3	50
Lowman	1952	43			30	70

The neuromuscular findings are frequent and helpful diagnostic clues in the disease, but the joint manifestations are more diverse and unreliable, and clinical and pathological data on these are sparse. There is a division of opinion as to the relative incidence of demonstrable mono- or polyarthritis (Table I). Boyd (1940a, b) found that polyarthritis with involvement of large joints or of all joints was very common; the joint symptoms in his cases, however, tended to fade into the background as the syndrome developed in its involvement of other systems. He states that, in his 100 cases, joints were the first system to be involved in nineteen and the second in eight (total, 27 per cent.), but he does not indicate whether this involvement was demonstrable as a synovitis or whether it was a subjective arthralgia. In the fourteen cases described by Jones (1942) the incidence of pain and/or joint swelling was 64 per cent. Spiegel (1936) reported articular prodromal symptoms in five of her seventeen cases, but again did not indicate whether there was any demonstrable synovial reaction. Articular swelling was noted in only four out of 29 new cases reported by Hench and others (1941).

Vining (1938) reported a case of periarteritis nodosa in a 7-year-old child in whom the initial onset was with joint swelling subsequent to acute tonsillitis; this patient was treated as a case of " acute rheumatism " for months before a biopsy diagnosis of periarteritis nodosa was established. Vining writes:

> From time to time there was swelling about several joints but this was thought due to nodal erythematous formation about the joint rather than synovitis.

Flexion deformities of arms and of shoulders did occur, however, in the course of 17 months.

In one of seven cases reported by Diaz-Rivera and Miller (1946) there was pain and soreness of one month's duration in the elbow, shoulder, and knee, as well as in the calf muscles.

A 15-year-old patient (Dunbar, 1936) presented with pain and swelling in both ankles with some increase in local heat, and was treated at first as a case of rheumatic fever before the establishment of a diagnosis of periarteritis nodosa.

A patient described by Carr (1930) had swelling of the knees, together with muscle pains in the feet and legs; the swelling, however, promptly subsided with bed rest and no mention is made of the objective state of the synovial tissue.

Weir (1939) reported a 30-year-old female patient with redness, swelling, stiffness, and pain in the elbows and wrists for 3 days before admission to hospital. Examination showed slight stiffness, tenderness, and pain on motion of the wrists, and " slight swelling " on the dorsal aspects; motion in the elbows was painful and these joints could not be fully extended. Again there is no indication of the amount of actual joint swelling.

In three of their six cases, Harris, Lynch, and O'Hare (1939) noted joint symptoms; one case presenting an acute migratory polyarthritis was treated with typhoid shots and ultimately recovered.

Moschowitz (1938) reports a patient with transient pains in the feet, who was at first diagnosed and treated as a case of arthritis before subsequent developments and biopsy proved periarteritis nodosa.

In the case reported by Curtis and Coffey (1934) there was a 6 months' period of weakness with swelling and pain in the ankles and feet; rest in bed relieved the swelling but not the pain. The swelling was attributed to oedema and the pain to neuritic involvement.

Only scattered cases have been reported wherein demonstrable evidence of synovial and joint changes have been noted. One patient (Hench and others, 1940) had marked articular changes and subcutaneous nodules resembling those of atrophic arthritis, and two others had atrophic arthritis; in all three instances periarteritis nodosa was proved at autopsy.

Investigations of pathological synovial changes in periarteritis nodosa have been even less frequent than clinical reports of joint manifestations. Bauer (1941) observed in one patient a marked synovitis with the typical vascular lesions noted elsewhere in periarteritis nodosa. Keefer (1943) felt that the pathological process was not limited to the vessels, but that granulomatous lesions could also be found in the organs including the joints, bursae, tendon sheaths, and connective tissue.

Results (Table II)

In thirteen of our 43 cases (30 per cent.), there were no symptoms referrable to the muscles, joints, or peripheral nerves.

In thirty cases (70 per cent.), muscle and joint symptoms were prominent early, but in only four (9 per cent.) did joint swelling appear with the joint pain.

In nineteen cases (44 per cent.), the muscle and joint symptoms were prodromal to development of a frank peripheral neuritis. In these nineteen cases, the appearance of peripheral neuritis helped to establish a diagnosis of periarteritis nodosa. In all but one case, sensory disturbances preceded the motor symptoms. These were variously described as a " burning ", " dull aching ", and " tenderness " of muscles, and involved feet, calves, and arms. Sharp, shooting pains were complained of by nine patients. Paraesthesias, hyperaesthesias, and numbness accompanied them or developed soon after, to be followed by subjective and objective motor weakness. Since the motor weakness was first evaluated subjectively, and since motor examination was not carried out before admission to the hospital, it is not possible to know whether an unrecognized weakness might not have been present from the start with the sensory disturbance. In twelve cases the feet and calves were the first parts to present symptoms of tenderness and pain; in six cases both upper and lower extremities were concurrently affected; and in only one were the upper limbs alone involved. In four cases the initial complaint was of orthostatic swelling in the ankles and lower legs.

In eleven cases (19 per cent.), there was muscle tenderness and arthralgia without subsequent development of peripheral neuritis. In all of these cases death intervened because of other causes (uraemia, pericarditis, cardiac failure, haemorrhage, dehydration, etc.).

TABLE II
SUMMARY OF RESULTS

Signs and Symptoms	No.	Per cent.
Muscle and Joint Symptoms	30	70
Joint Swelling	4	9
Peripheral Neuritis ..	19	44
Total Patients ..	43	100

Arthralgias when present were generally migratory without swelling; in one case pain without swelling persisted in a knee for 10 days. Generally the muscle aching was worse with activity and better with rest. Muscles were tender to palpation, and in two cases a diagnosis of dermato-myositis was entertained and was not disproved until necropsy examination. In only one case out of the entire group were the muscle symptoms suggestive of a fibrositis. The muscle symptoms varied from vague aching in the neck and back to intense pain involving all four extremities and requiring codeine 4-hourly.

In four cases (9 per cent.) with joint pain there was objective evidence of neuritis. Three of these subsequently progressed to a peripheral joint swelling early in the disease, and in one additional case there was questionable joint swelling that predominated in the clinical picture.

In one 30-year-old male patient who had had episodes of rheumatic fever at the ages of 8 and 22 years, there was pain initially in the left arm, followed by migratory joint symptoms in feet, hips, left elbow, wrist, and hand, and right big toe (which last, became swollen and sore). Another patient had an initial acute

polyarthritis with swelling, pain, and " stiffness " of many joints for one month before muscle symptoms of constant aching and diffuse tenderness dominated the clinical picture. A third patient, 10 weeks after an acute sore throat, developed swelling and tenderness of the hand. This swelling persisted for 2 weeks; 4 weeks later he developed fever, abdominal pain, and muscle wasting, and finally died in convulsions.

In a fourth patient who had profound systemic symptoms and peripheral neuropathy, the left knee became painful without objective evidence of synovitis, and this persisted for 10 days before death. The synovia from this case was examined histologically, and vascular lesions were seen identical with those encountered elsewhere (Fig. 1). Involvement was spotty; the synovia histologically showed only a moderate increase in fibroblastic activity, mild oedema, and fibrous thickening (Fig. 2). There was no cellular cuffing of smaller vessels and no cellular inflammatory exudate despite the severe arterial changes.

Comment

The organic damage resulting from periarteritis nodosa is directly related to the degree of impairment of blood supply to the organ. Since periarteritis nodosa involves the vascular tree spottily, the organic damage is manifested patchily. The degree of ischaemic necrosis (or infarction) resulting in an involved part will largely depend upon the availability of a collateral blood supply; organs supplied by end arteries would be expected to suffer to the greatest degree from vascular involvement. Conversely, in locations of abundant collateral circulation, more extensive vascular damage would be required to cause a similar degree of ischaemia or infarction.

Since the synovial tissue is abundantly supplied with vessels it would be expected that involvement to a demonstrable degree in this tissue would be unusual, and such seems to be the case. While arthralgias are common, extensive synovitis or arthritis are uncommon. The arthralgias probably represent small localized areas of involvement, demonstrable histologically and subjectively but not by gross objective examination of the joint. This differs from the panvasculitis observed in synovia from cases of lupus erythematosus and from the extensive inflammatory synovitis of rheumatoid arthritis. It seems reasonable that in the rare case of periarteritis nodosa there might be extensive enough vascular involvement in the synovia of a joint to produce a more extensive process, but statistically this proves to be infrequent.

Though cases of atrophic arthritis in which periarteritis nodosa was later proved at autopsy have been reported, it cannot be assumed that the two conditions were points of the same process; it would be wiser to assume that the two separate disease phenomena co-existed in the same patients.

Oedema of dependent parts seems not uncommon in cases of periarteritis nodosa. The cause of this is unknown unless it be a manifestation of the peripheral neuritis. Soft tissue oedema, together with muscle soreness and tenderness, may prove misleading to one unaccustomed to evaluating synovial reactions in joints, and an erroneous impression of " arthritis " might be entertained. Careful examination

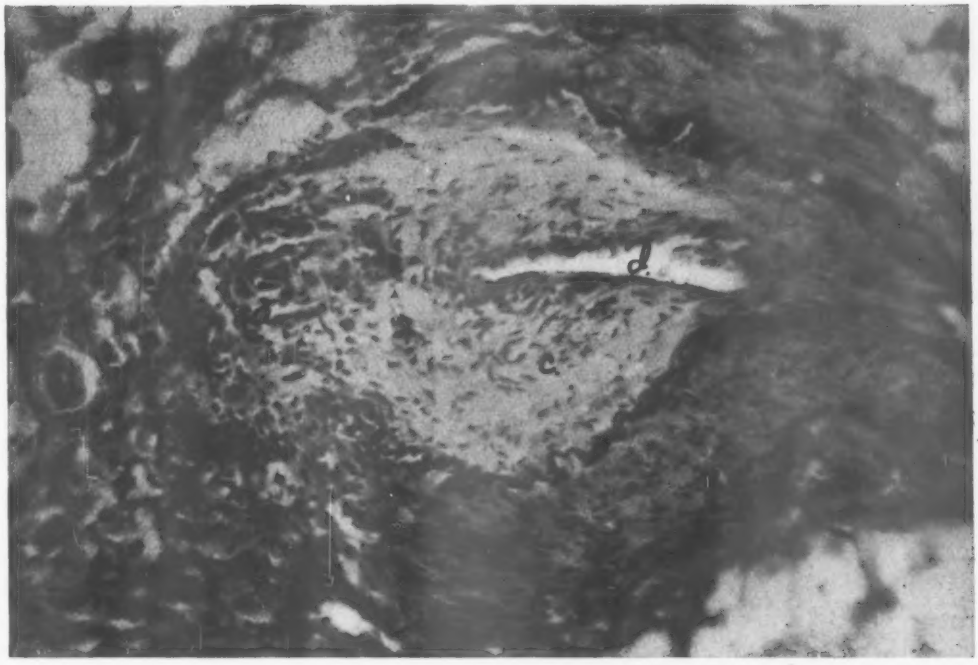

FIG. 1.—Synovial artery showing (*a*) granulomatous stage of arteritis with (*b*) disruption of elastic lamina, (*c*) reactive intimal thickening, and (*d*) encroachment upon vessel lumen. (Elastic Van Geison.)

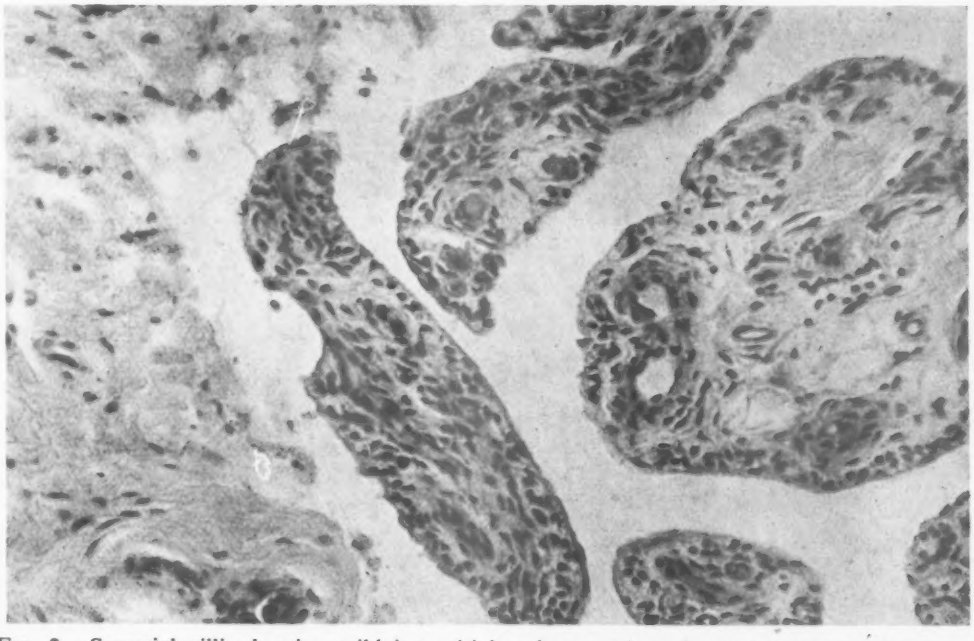

FIG. 2.—Synovial villi, showing mild interstitial oedema and moderate increase in fibroblastic activity. (Haematoxylin and eosin.)

is therefore of the greatest importance, especially in those early cases wherein the neuromuscular system changes may be the only manifestations to assist diagnosis.

Conclusions

(1) Tender, aching muscles and arthralgias are common early manifestations of periarteritis nodosa. These become worse with activity, improve with rest, and differ clinically from fibrositis.

(2) Synovial vascular changes are identical with those seen elsewhere in the disease, but synovitis of a grossly demonstrable degree is infrequent; when it occurs, it assumes a less important part in the more profound pathological picture.

(3) Muscle tenderness and arthralgias are commonly the prodromata of a more ominous peripheral neuropathy.

Summary

Forty-three cases of periarteritis nodosa have been reviewed and the joint and muscle manifestations evaluated.

In thirty (70 per cent.) of the cases, muscle and joint symptoms were the early complaints. In only four cases, however, was there objective evidence of synovial involvement and in no case was joint involvement a major aspect of the clinical picture. Histological study of synovia showed arterial involvement identical to that seen elsewhere in the disease, with spotty synovial change secondary and proportionate to arterial involvement.

Muscle tenderness and aching were common early manifestations, but in only one case were the symptoms suggestive of fibrositis, the muscle symptoms being worse with activity and better with rest. In nineteen cases, there was progression to frank peripheral neuritis.

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Manifestations articulaires et neuromusculaires de la périartérite noueuse

Résumé

On étudia 43 cas de périartérite noueuse et on évalua les manifestations articulaires et musculaires.

Dans 30 cas (70%) les symptômes musculaires et articulaires apparurent précocement. Toutefois, dans quatre cas seulement il y eut des preuves objectives d'implication synoviale, et l'atteinte articulaire ne constitua jamais l'aspect majeur de l'image clinique. L'étude histologique de la

synoviale montra que l'atteinte artérielle y était identique à celle observée ailleurs au cours de la maladie, avec des modifications synoviales d'aspect tacheté, secondaires, et proportionnelles à l'atteinte artérielle.

La sensibilité musculaire et la douleur constituaient des manifestations précoces communes, mais dans un cas seulement il y avait des signes indiquant une fibrosite, les symptômes musculaires étant plus accentués au mouvement et s'améliorant au repos. Dans 19 cas il y avait une évolution franche vers la névrite périphérique.

Manifestaciones articulares y neuromusculares de la periarteritis nodosa

SUMARIO

Cuarenta y tres casos de periarteritis nodosa fueron revisados y sus manifestaciones articulares y neuromusculares valoradas.

En 30 casos (70 por ciento) los síntomas musculares y articulares se manifestaron precozmente. Sin embargo, en cuatro casos solamente hubo pruebas objetivas de la implicación de la sinovia y en ningún caso la afección articular constituyó un aspecto mayor del cuadro clínico. El estudio histológico de la sinovia mostró alteraciones arteriales idénticas a las encontradas en otras partes en esta enfermedad, con el aspecto moteado secundario y proporcional a la implicación arterial.

La sensibilidad y el dolor muscular constituían manifestaciones tempranas comunes, pero en un caso sólo había síntomas indicando una fibrositis, los síntomas musculares siendo peores con actividad y mejores con reposo. En 19 casos hubo evolución franca hacia una neuritis periférica.

PERIOSTITIS DEFORMANS*

BY

M. SORIANO

The Medical School, Barcelona, Spain

(RECEIVED FOR PUBLICATION FEBRUARY 25, 1952)

In the course of 3 years we have been able to study six patients presenting similar clinical, radiological, and pathological features, which demonstrate the existence of a hyperostosing poliostotic disease, not hitherto described, which extends to the whole skeletal system except the skull, and which we have named " periostitis deformans ".

Main Characteristics

(1) Clinical.—This is an acquired disease, of primary type, which recurs with varying intensity. Osseous tumours rapidly develop as a result of an intense exuberant osteogenic periostitis. Inflammatory manifestations are very rare, and if they do appear, are very discrete. The activity of these outbreaks of periostitis ceases within 2 to 12 months, and the patient then recovers his health, but the bony deformities remain as sequelae, though some of the osseous tumours may undergo total involution. These attacks may recur during the whole life of the patient, but they tend to be less intense each time. They are usually indolent in type, but are sometimes accompanied by pain that ceases once the osteophytes or affected periosteal tissues cease to grow. The more intense outbreaks are accompanied by a toxic appearance, with anorexia and wasting, which subsides once the attack has passed. There is no fever. The skin covering the bony pseudotumoral nodules becomes slightly thickened during the outbreak phase, but only rarely presents inflammatory signs. The outbreaks usually end by the

* Summary of a monograph published under the same title, Editorial Paz, Madrid, 1952.

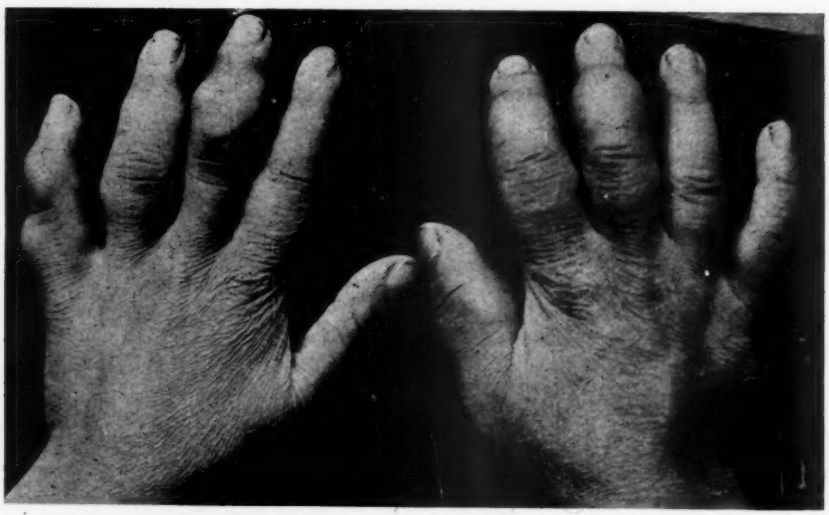

FIG. 1.—Case 1, appearance of hands 8 months after initiation of deforming periostitis.

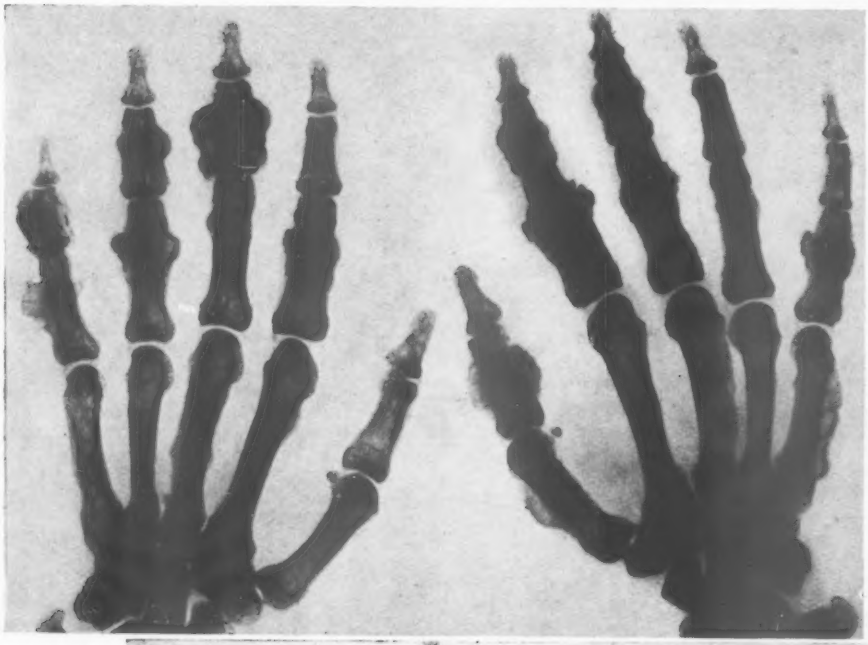

FIG. 2.—Case 1, *x*-ray of hands as in Fig. 1.

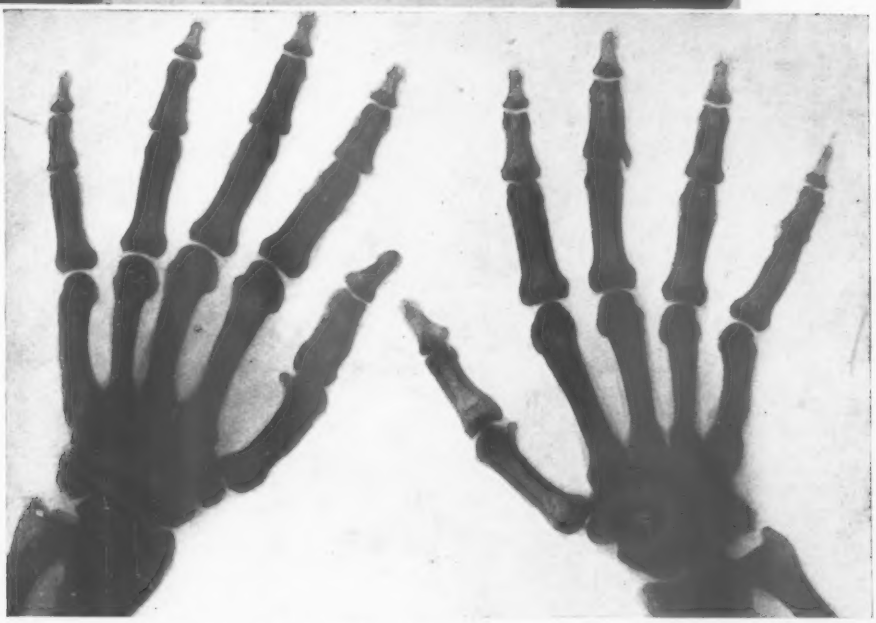

FIG. 3.—Case 1, *x*-ray of hands one year later.

involution of the osseous growths; a local periostitis may remain as a sequel, but there is never any suppuration, necrosis, or tumoral degeneration. The periosteal growth around the joints may cause functional loss of power which is sometimes very marked.

Many outbreaks pass off without clinical recognition and are only revealed in the radiographs which show definite superimposed layers of periostitis corresponding to the successive attacks (Fig. 5).

(2) Anatomical.—The lesions are poliostotic and frequently symmetrical; they affect the spinal column only slightly, and the skull not at all. The bones become

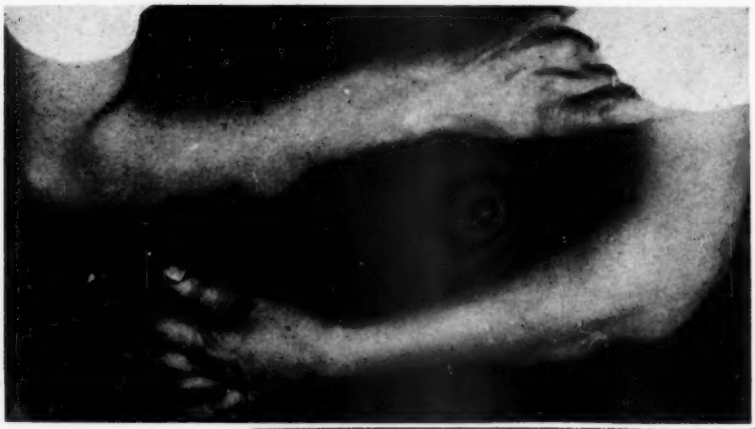

FIG. 4.—Case 1, Deformities of forearms and elbows during a second outbreak some months later.

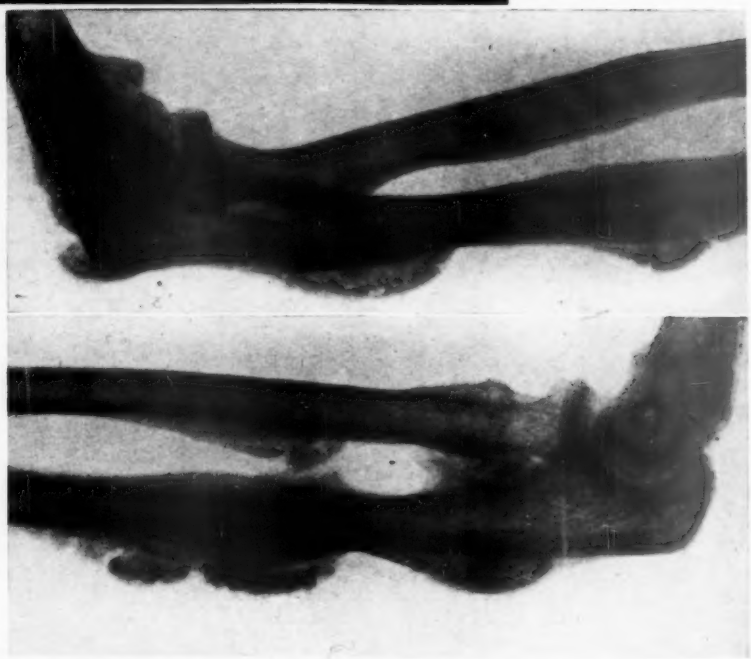

FIG. 5.—*X*-ray of forearms as in Fig. 4. A layer of periosteal ossifying proliferation of recent appearance has developed on an old zone of periosteal enlargement remaining as a sequel of previous attacks.

surrounded by a layer of ossified thickened periosteum with exuberant exostosis of irregular form, which in very severe cases forms true bony outgrowths, causing thickening and marked deformity of the bones and peri-articular regions (Fig. 4).

(3) Histological.—An ossifying periosteal proliferation is observed; it first produces bone of embryonic type and this soon develops into adult bone (Fig. 6).

Almost immediately a process of osseous reabsorption begins, and abundant osteoclasts advance from below to invade the germinative layer of the periosteum, producing a spongy bone of dense mesh-work (Fig. 7). Subsequently, in this newly-formed bone, an intense osteoporosis is seen with reabsorption of the osseous tumour; this may disappear entirely (Fig. 3) though it more frequently remains as a more or less osteoporotic hyperostosis (Figs 11, 12, and 13). Before reaching the quiescent phase, the osteoblastic process, in association with the osteoclastic, takes on a mosaic-like appearance which is later replaced by an

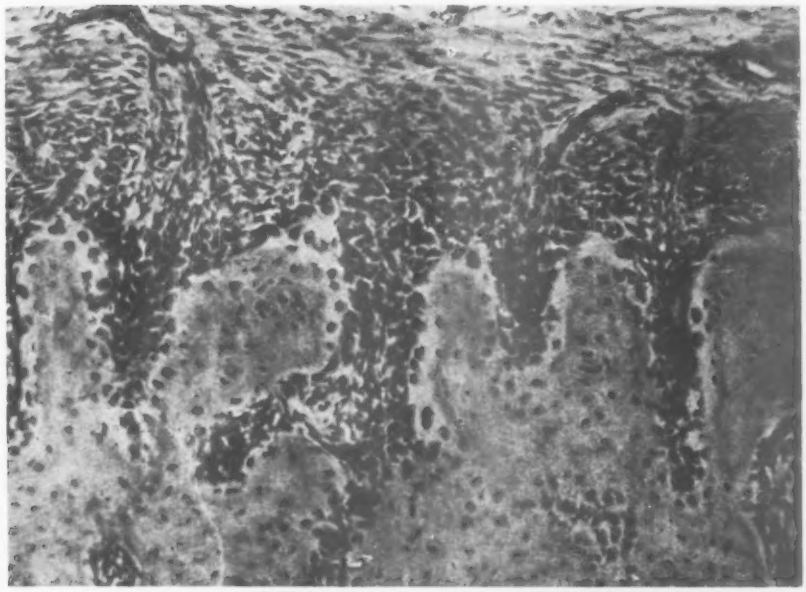

FIG. 6.—Deforming periostitis with intense periosteal proliferation and compact bone formation (high magnification).

FIG. 7.—Periostitis in the advanced phase with spongy osseous tissue formation and abundant osteoclastic function.

osteoporotic osseous tissue. This remains quiescent (Figs 8 and 9) until a new periosteal outbreak provokes the apposition of a new layer of osseous efflorescence, which follows the same histological evolution as the previous one.

In normal bone, an osseous condensation and eburnation is first established, and this is followed by an osteoporosis each time more marked.

The walls of the vessels that cover the periosteum present a thickening and slowly progressive hyperplasia which in advanced phases is very marked (Fig. 8).

(4) Radiological.—The *x*-ray photographs present four characteristic appearances:

(*a*) *Periosteal Thickening.*—This extends in the form of a layer that covers the bone with exuberant growths of capricious form.

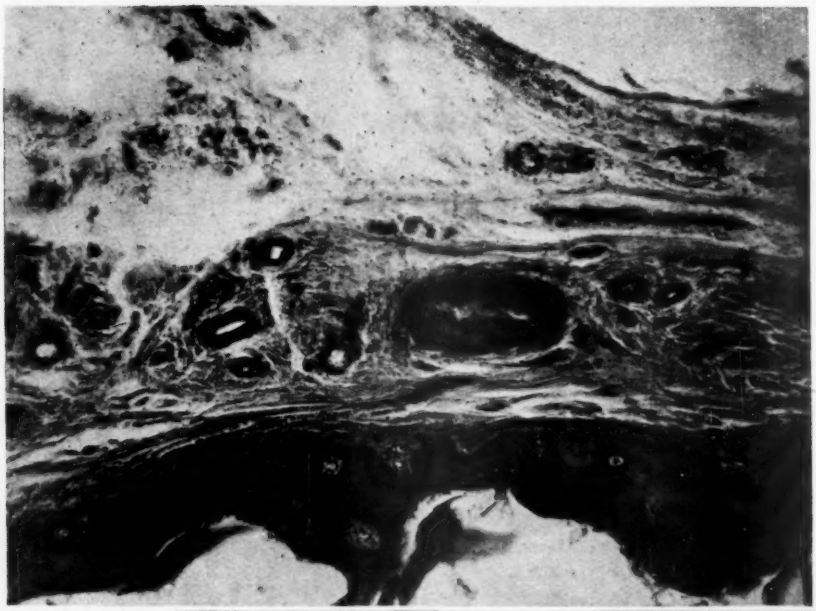

FIG. 8.—Newly-formed osseous tissue in the quiescent terminal phase of advanced osteoporosis with enlargement of periosteal vessels.

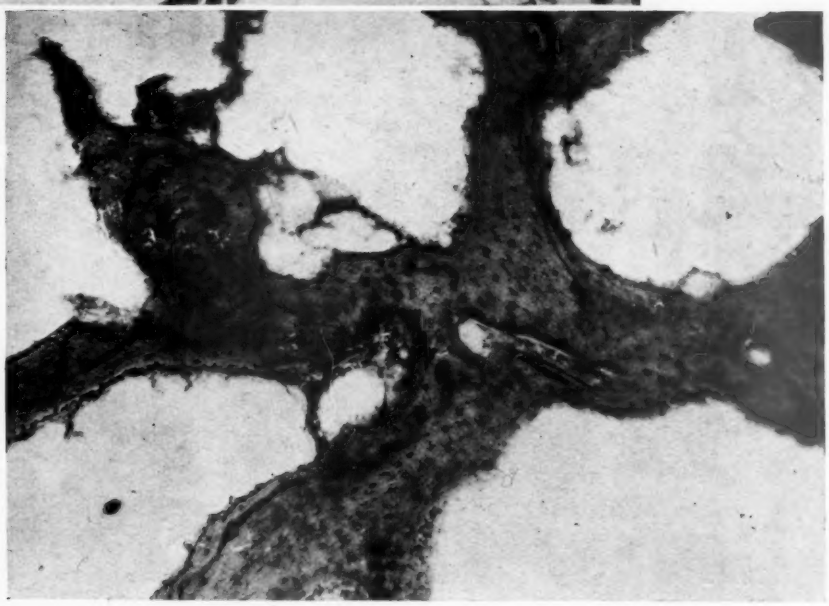

FIG. 9.—Newly-formed osseous tissue in the terminal phase of advanced osteoporosis (high magnification).

(*b*) *Osteophytes or Osseous Nodules.*—These are of rapid growth; they develop on the diaphysis and in 2 to 10 months may reach the size and shape of a chick-pea or almond on the fingers, of a hazel or walnut on the forearms and elbow, and of an egg or mandarin orange on the femur.

(*c*) *Peri-articular Alterations.*—These develop around the joints in the form of osteophytes.

(*d*) *Osseous Alterations.*—At first a diffuse bony condensation is seen, and this is followed by the appearance of osteoporotic zones, larger each time, until the whole bone is invaded. In some places the cortical layer of bone underlying the hyperostosis remains striated, thickened, and porotic, suggestive of Paget's disease.

FIG. 10.—Case 2, Roentgenogram of forearm showing lesions in the spongy ossification phase initiating osteoporosis.

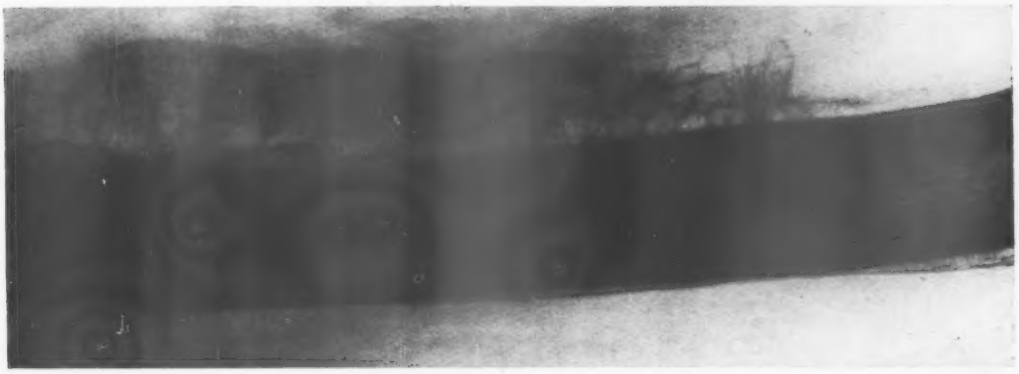

FIG. 11.—Case 3, Roentgenogram of femur showing large osteophytes in the advanced phase of osteoporosis.

The radiological structure of the osteophytes passes through three stages:

(*i*) *Embryonic Bone.*—This gives a faint radiological shadow with the appearance of an efflorescence that takes on a cockade or cauliflower shape as it grows (Fig. 2).

(*ii*) *Spongy Bone.*—This is seen as a sponge-like structure of dense meshes with indented or very irregular edges (Fig. 10).

(*iii*) *Osteoporotic Bone.*—This produces wide transparent meshes with smooth edges of capricious form.

(5) Haematological.—Patients so affected have a tendency to present hyperproteinaemia, the Weltmann coagulation test is shortened, and the erythrocyte sedimentation rate is occasionally raised. The serum alkaline phosphatase is always increased. Blood calcium and phosphorus are normal. There is no anaemia and the number of leucocytes is normal. Frequently a slight but definite lymphocytosis and monocytosis is observed.

Course of the Disease

Pathogenesis.—We suppose that this disease is due to a toxi-allergic action of tuberculous origin, only affecting constitutionally predisposed individuals who have in their osseous development a deficiency such as corresponds in other patients to the presentation of congenital osseous malformations. This form of *skeletal infantilism* is seen in the small size of all the patients, which is frequently combined

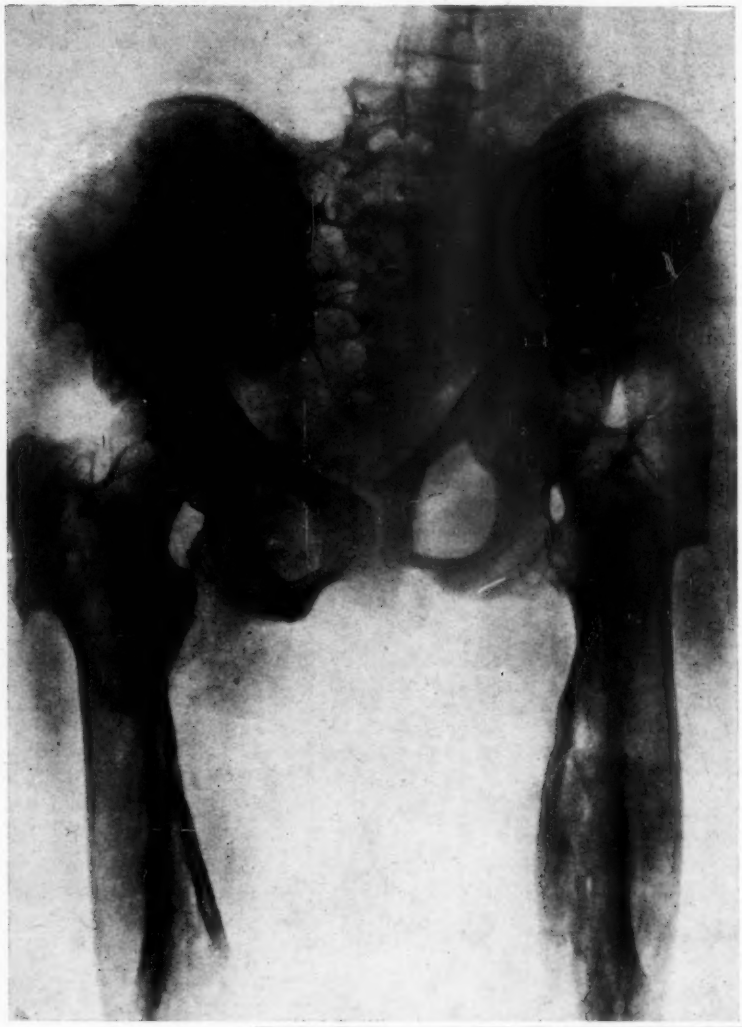

FIG. 12.—Case 5, Pelvis and upper half of femur showing marked residual lesions of deforming periostitis.

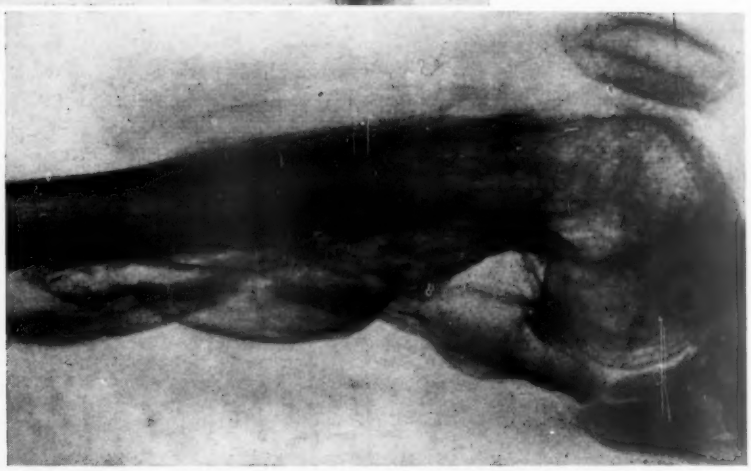

FIG. 13.—Case 5, Lower half of femur.

with an infantile psychopathic personality. Because of this fact of predisposition, the disease may present itself in various members of the same family.

Evolution.—The hyperplastic periostitis always appears to end favourably after a period of 4 to 12 months, but it then leaves as sequelae osseous deformities, with functional difficulties in some joints, and osteoporosis. The outbreaks may recur throughout the patient's life, though each attack is usually less intense. Though the lesions are poliostotic, in some cases they are more localized in forearms and hands, and in others in the bones of the leg.

Treatment

We have no knowledge of a curative medication of the outbreaks, nor have we been able to prevent relapses. It is possible that nitrogen mustard may be found to have a favourable action. The treatment of the sequelae by vitamin D and calcium is important, as well as the resection of any particular osseous bulgings that may hinder the movement of the limbs when present in very accentuated forms.

Summary

(1) The clinical, radiological, haematological, and histological characteristics of a type of bone deformity are described and illustrated with reference to the appearances in six patients observed during the past 3 years.

(2) The disease may be classified as hyperplastic osteogenic recurrent osteoperiostitis, of polyostotic type, with pseudotumoral exuberant development of primary nature and specific character. It is probably tuberculous in origin, but seems to require certain predisposing conditions in the skeletal development.

(3) Forms of treatment are suggested, but no method of cure has yet been found.

Périostite déformante

RÉSUMÉ

(1) On décrit et on illustre les caractères cliniques, radiologiques, hématologiques, et histologiques d'un type de déformation osseuse se rapportant à l'apparence de six malades observés pendant les trois dernières années.

(2) On peut définir cette maladie comme une ostéopériostite ostéogène hyperplasique recurrente du type polyostique, avec un développement exubérant pseudo-tumoral de nature primaire et de caractère spécifique. Elle est probablement d'origine tuberculeuse, mais semble exiger certaines conditions prédisposantes dans le développement du squelette.

(3) On suggère des formes de traitement, mais on ne connait pas de cure.

Periostitis deformans

SUMARIO

(1) Se describen, ilustradas, las características clinicas, radiologicas, hematológicas e histológicas de un nuevo tipo de deformidad ósea, que ha sido observada en seis pacientes durante los últimos tres años.

(2) La enfermedad puede clasificarse como una osteoperiostitis hiperplásica osteogenética de curso recurrente y de extensión poliostótica, con desarrollo exuberante pseudotumoral, de naturaleza primaria y de carácter específico. Es probable su origen toxi-tuberculoso, pero parece requerir ciertas condiciones predisponentes en el desarrollo esquelético.

(3) Se sugieren algunas formas de tratamiento, pero no se ha encontrado ningún método curativo eficaz.

ANAEMIA OF RHEUMATOID ARTHRITIS*

BY

M. R. JEFFREY

From the Rheumatism Research of the South West and Oxford Regions, Royal National Hospital for Rheumatic Diseases, Bath

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It has long been recognized that anaemia is a common feature of rheumatoid arthritis. Garrod (1876) who introduced the term " rheumatoid arthritis ", noted the association. Much more recently, the report of the Scientific Advisory Committee of the Empire Rheumatism Council (1950) has provided evidence of a frequent and important relationship.

Although this anaemia is usually not very severe, it is frequently refractory to all forms of treatment. The introduction of iron preparations suitable for intravenous injection has considerably reduced, but by no means abolished, the problem of cases refractory to treatment (Sinclair and Duthie, 1950; Ross, 1950).

Very little attention has been paid to the causes and nature of this anaemia. Apart from one monograph by Nilsson (1948), no comprehensive investigation has been attempted. We therefore felt it worth while to examine this anaemia in some detail; the results obtained are presented below.

Results

Peripheral Blood.—The first step was to study the morphological characters of the anaemia and the cellular composition of the red bone marrow. The anaemia was found to be essentially normocytic and hypochromic. Red cell size, as shown by the mean corpuscular volume (M.C.V.) was normal in 48 of the 65 cases studied; the values in the other cases were distributed equally above and below the normal range and were almost certainly due to inaccuracies in the red cell count rather than to the rheumatoid arthritis.

On the other hand, the haemoglobin concentration in the red cell was almost invariably diminished; only five out of 136 cases examined gave a normal value for mean corpuscular haemoglobin concentration (M.C.H.C.).

It is interesting to compare the relative importance of reduction in the number of circulating red cells and of reduction of the haemoglobin concentration in the red cells in producing anaemia. In our cases, the average red cell count was about 15 per cent. below the normal average value in both sexes. The average reduction of M.C.H.C. below the normal mean was also about 15 per cent. It appears therefore that reduction in the number of circulating red cells may be more important in producing anaemia than has been generally recognized.

By dividing the cases into clinical groups according to the activity of their rheumatoid disease, it was evident that the lowest average values for red cell counts, haemoglobin, and M.C.H.C. were found in the cases with very active disease (see Table, opposite). The M.C.V. on the other hand, showed no consistent change in the various activity groups.

The cases were also divided into groups according to their age and the duration of their disease; neither of these factors, however, appeared to have a significant effect upon the degree of anaemia.

Evidence of Undue Haemolysis.—In about fifteen cases we sought evidence of undue haemolysis by estimating plasma bilirubin, faecal urobilinogen, and reticulocytes; all

* Paper read to the Heberden Society on December 7, 1951.

TABLE

Sex	Male			Female		
Activity Group	1	2	3	1	2	3
R.B.C. (mill./c.mm.)	4·70	4·50	3·70	4·52	4·07	3·93
Hb (g./100 ml.)	13·2	12·1	10·9	11·3	10·8	9·6
M.C.H.C. (per cent.) ..	29·9	29·7	28·8	29·2	28·9	28·0

Notes. (*i*) Activity Group 1=slightly active, 2=moderately active, 3=very active disease.
(*ii*) All figures represent mean values.
(*iii*) Differences between the means given by activity Groups 1 and 3 are statistically significant in all cases except the male values for M.C.H.C.

these tests gave normal results. The red cell fragility was also tested in a few cases; the only abnormality found was an increased resistance to haemolysis in some cases, a not infrequent phenomenon in any variety of hypochromic anaemia. We concluded, therefore, that undue haemolysis was not of material importance in this anaemia.

Red Bone Marrow.—Haemopoiesis in the red bone marrow was studied in sixteen cases by examination of stained smears of marrow juice withdrawn by sternal puncture. No regular major change was found, though there were one or two points of interest. The myeloid series was almost entirely normal; we observed neither the " hypocellularity " found by Merlo and Tortori-Donati (1945), nor the " global granuloblastic hyperplasia " described by Luchesi and others (1946): the most our cases achieved was a slight increase of metamyelocytes. As regards the red cell series, only one female case showed well-marked normoblastic hyperplasia. This woman improved considerably during her stay in hospital, her arthritis becoming much less active and her haemoglobin rising from 50 to 85 per cent., here the hyperplasia was apparently spontaneous, the result of a natural remission in the rheumatoid disease. The other cases showed essentially normal proportions of normoblasts, though, in view of the fact that all the patients were distinctly anaemic, the marrows showed less evidence of activity than might have been expected. The majority of the normoblasts had a polychrome cytoplasm; few had acquired a normal haemoglobin content even at a late stage of nuclear maturation. Our findings agree, therefore, with those of Nilsson (1948, p. 99), who observed disturbance of haemoglobin formation in the normoblasts. It is of interest too that about half of our cases showed a relative diminution of the more mature normoblasts and that these cases had red cell counts in the peripheral blood which were distinctly below the counts of the cases with normal proportions of primitive red cells. There is a suggestion, therefore, that disturbance of normoblast production may play a part in producing this anaemia.

Another minor point of interest concerns the megakaryocytes. Normally, about two-thirds of these cells show clear evidence of platelet production, platelets being budded off from the edge of the cell. The proportion is markedly decreased in idiopathic thrombocytopenic purpura, which is ascribed by Dameshek and Miller (1946) to " hypersplenism ". Four of our cases showed a decreased proportion of actively budding megakaryocytes, and it is conceivable that these four cases were also examples of mild " hypersplenism ". The reports that occasional cases of rheumatoid arthritis improve considerably after splenectomy (Bach and Jacobs, 1951) raise the question whether there is any correlation between the marrow cytology and the result of the operation, and whether in fact it may be possible to select cases suitable for the operation by examination of marrow smears.

Blood, Plasma, and Corpuscle Volumes.—The suggestion of Robinson (1943), that dilution of the blood by an increased volume of plasma might produce apparent anaemia in rheumatoid arthritis, was investigated by estimating the plasma volumes of fifty cases, using the Evans blue method of Gregersen (1944). The detailed figures will be published elsewhere;

it may, however, be said that the results did not support the idea of haemodilution. In fact, volume changes fitted in with those defined by Gibson and Evans (1939) in a variety of types of anaemia, namely, a reduction in the total mass of circulating red cells and in the whole blood volume with a normal plasma volume.

Iron Metabolism.—Cartwright and others (1946) have shown that the concentration of iron in the plasma is reduced during infection or experimental inflammation. Nilsson (1948, p. 62) found a similar reduction in cases of rheumatoid arthritis, and our observations agree with his. The plasma iron was below normal in 156 of the 200 cases which we examined. Women exhibited low values rather more frequently than men and the average value for the women was considerably lower. There was a tendency for the cases suffering from the most active rheumatoid disease to exhibit the lowest plasma iron values. In very active cases, and in those who were markedly anaemic, lowering was invariable.

We did not observe any consistent change in the plasma iron as a result of cortisone or ACTH therapy when these substances were given for relatively short periods, not exceeding 3 weeks.

The plasma iron is, of course, raised by intravenous iron therapy and quite frequently remains raised above its initial value for a period of weeks or months, even in cases who show no material increase in haemoglobin. From the cases so far observed, it appears that the degree or duration of this persistent rise in plasma iron (as distinct from the very large and transitory increase immediately following injection) bears little relation to any increase which may occur in the haemoglobin value. The plasma iron does, however, become normal after therapy only in those whose haemoglobin level becomes normal.

There is good evidence, therefore, that iron metabolism is altered in rheumatoid arthritis. From the clinical point of view, cases who become anaemic may be divided into three categories:

(*a*) Those who respond rapidly and completely to iron by mouth; this is a small group with the characteristics of ordinary iron deficiency anaemia, in whom the occurrence of anaemia and rheumatoid arthritis may well be coincidental.

(*b*) Those whose anaemia is entirely refractory to all haematinics; this probably represents the real anaemia of " rheumatoid arthritis " about whose origins our knowledge is fragmentary.

(*c*) Those whose anaemia is refractory to iron by mouth but responds completely, or to a material extent, to intravenous iron.

There are three obvious explanations for the occurrence of this third group (*c*). The intestinal absorption of iron might be greatly impaired; the mechanism for transporting iron from the intestine to the tissues might be inefficient; the absorbed iron might be rapidly removed from the blood stream by some non-haemopoietic tissue and thus prevented from taking part in blood formation.

(*i*) *Iron Absorption.*—To try and assess the efficiency of intestinal absorption, we investigated the changes in plasma iron in twenty cases after a single test dose of iron by mouth. The subjects were given 9 gr. ferrous sulphate, the largest dose commonly employed therapeutically, together with 250 mg. ascorbic acid to preserve the iron in the reduced form and to minimize the effects of a possibly altered gastric secretion.

The amount of the maximal increase in the plasma iron after this test dose varied greatly among the cases; they can, however, be divided roughly into three groups, of which the two extremes are of interest.

(*a*) In three women, a very large increase in plasma iron followed the test dose, the concentration rising from a markedly low level in the region of 30 μg. to about 400 μg./100 ml. These women were subsequently given ferrous sulphate therapeutically by mouth and all responded well, their haemoglobin values rising to normal within 6 weeks. This first group, then, showed excellent absorption and undoubtedly suffered from simple iron deficiency anaemia.

(*b*) At the other extreme were eight cases in whom only a very small increase in plasma iron concentration followed the test dose, an increase insufficient to raise the initially low plasma iron value into the normal range. There was no evidence of the general tendency for anaemia to increase iron absorption, but rather a suggestion that this function was impaired.

The failure of the plasma iron to rise does not, of course, prove that the absorptive function of the intestine is at fault, for there are at least three other possible explanations: that the iron was not available to the intestine for absorption, that the tablets had not dissolved, or that the iron had formed some not readily ionized compound. Against these possibilities are the facts that in all cases the stools were blackened by the test dose of iron, and that, as the patients had fasted overnight before the test, the upper small intestine should have been free of any food which might have reduced the availability of the metal. In these circumstances, ascorbic acid is very effective in preserving iron in the reduced state available for absorption (Moore and others, 1939). It therefore seems unlikely that conditions within the intestine played a large part in reducing iron absorption.

(*ii*) *Iron-Transporting Protein.*—A second possible explanation of the failure of the plasma iron to rise after the test dose is that, though absorption from the intestine occurred normally, the transporting mechanism in the plasma was unable to carry the metal. Iron is carried in the blood stream by a specific protein, a β globulin. Rath and Finch (1949) developed a method for the photometric estimation of this protein in terms of its iron-carrying capacity, based on the fact that the iron-protein complex possessed a characteristic pinkish colour. Using this method, we investigated fifty cases of rheumatoid arthritis, of various degrees of anaemia and severity, and found no essential abnormality. The average values were almost identical with those of Rath and Finch's normal subjects and, though the range in the rheumatoid cases was slightly greater than normal, in no case was there a reduction present which could have interfered with the transport of absorbed iron. Thus the transport mechanism is intact in rheumatoid arthritis.

(*iii*) *Abnormal Removal of Iron from the Plasma.*—A third possible explanation of the failure of the plasma iron to rise after the test dose is that the absorbed iron was very rapidly removed from the blood stream. There is evidence that, in the presence of inflammation, iron given intravenously is unusually rapidly removed from the blood stream, and Nilsson (1948, p. 141) has shown that this holds true in rheumatoid arthritis. Nevertheless, the rate of removal in Nilsson's cases was not very greatly increased, nor has it been found to be so in the few cases which we have so far studied. It is difficult to believe that in our cases the removal mechanism was adequate, or was sensitively enough adjusted, to prevent a rise of more than 35 μg. in the plasma iron concentration in the face of normal absorption—as in fact happened in six of the twenty cases studied.

It seems, therefore, that there is at least a strong possibility that impaired absorption accounts for the superiority of intravenous over oral iron therapy in some cases of rheumatoid arthritis. It is worthy of note that therapeutically iron is usually given by mouth in circumstances which would tend still further to reduce absorption, for the dose is often less than the present test dose and is given after food without ascorbic acid.

The present investigations shed no light on the possible role of impaired absorption in producing anaemia in rheumatoid arthritis. In the day-to-day absorption of iron from food, quantities are involved of the order of 1 mg., and alterations in gastric secretion and intestinal contents may well be important. This is, therefore, a separate problem from that of the absorption of therapeutic doses, and it is one on which we hope to begin work shortly.

Summary

(1) The anaemia of rheumatoid arthritis is normocytic and hypochromic, its severity running roughly parallel with the degree of disease activity.

(2) The anaemia is not haemolytic.

(3) The sternal marrow is not grossly abnormal but gives some evidence of disturbed haemoglobin formation and normoblast production.

(4) The plasma volume is normal; in the more anaemic cases, whole blood and corpuscle volumes are reduced.

(5) The plasma iron is usually reduced, but the iron transport mechanism of the plasma is unimpaired.

(6) Part of the anaemia is often due to iron deficiency; impaired intestinal absorption and other factors are probably usually responsible for the failure of oral iron therapy.

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Anémie de l'arthrit rheumatismale

Résumé

(1) L'anémie de l'arthrite rhumatismale est normocytique et hypochromique, et sa gravité est à peu près proportionnelle à celle de l'activité morbide.

(2) Cette anémie n'est pas hémolytique.

(3) La moelle sternale, sans être franchement anormale, présente quelques indications de la formation defectueuse de l'hémoglobine et des normoblastes.

(4) Le volume du plasma est normal; dans les cas d'anémie plus prononcée le volume sanguin total et corpusculaire se trouvent diminués.

(5) Le fer plasmatique est généralement diminué, mais le mécanisme du transport de fer par le plasma n'est pas affecté.

(6) L'anémie est souvent due partiellement au manque de fer; les échecs de la thérapie martiale par voie buccale sont généralement dus à un défaut de l'absorption intestinale ou à d'autres facteurs.

La anemia de la artritis reumatoide

Sumario

(1) La anemia de la artritis reumatoide es normocítica e hipocrómica, y su gravedad corresponde aproximadamente a la de la actividad morbosa.

(2) Esta anemia no es hemolítica.

(3) La médula esternal no es muy anormal pero presenta algunas indicaciones de perturbación de la formación hemoglobínica y normoblástica.

(4) El volumen del plasma es normal; en los casos muy anémicos el volumen total y corpuscular están reducidos.

(5) El hierro plasmático está generalmente reducido pero el mecanismo plasmático de transporte del hierro no está afectado.

(6) En parte, la anemia es a menudo ferripriva; un defecto en la absorción intestinal y otros factores constituyen probablemente la causa de los fracasos de la ferriterapia por via oral.

CORTISONE IN THE TREATMENT OF DEGENERATIVE JOINT DISEASE OF THE HIP*

BY

WILLIAM F. DOWDELL, WALTER M. SOLOMON, ROBERT M. STECHER, and RALPH WOLPAW

From the Department of Medicine, Western Reserve University School of Medicine, at Cleveland City Hospital, Cleveland, Ohio

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Degenerative joint disease of the hip, often called osteo-arthritis, or malum coxae senilis, a clinical condition known for the pain and deformity it causes, is the most disabling form of degenerative joint disease.

The cause of the condition is unknown; trauma, an old dislocation of the hip, a slipped epiphysis, Legg-Perthes disease, and senescent degenerative changes have all been suggested (Steindler, 1951) as the most likely factors in its formation.

The pathology comprises fibrillation, erosion, and eburnation of the articulating cartilage and the production of exostoses of bone. The femoral head may show variable degrees of flattening, and cystic changes may be localized in it as well as in the acetabulum. Sclerosis of the acetabular rim is also seen. Later fibrosis of the joint capsule and peri-articular tissue may also occur and lead to further restriction of joint mobility.

Because of the dramatic effects of cortisone in rheumatoid arthritis, its use experimentally in malum coxae senilis seemed worthwhile even though the pathology of the latter disease differs markedly from that of rheumatoid arthritis. This series of experiments was also prompted by the differences in clinical results following treatment of degenerative joint disease (including malum coxae senilis) with ACTH and cortisone as reported in the literature. Hench and others (1950) reported a patient with degenerative joint disease of one knee who received cortisone for the treatment of leukaemia cutis, and noted relief of pain and stiffness of the involved knee. Boots and others (1951) reported the treatment of eleven patients with malum coxae senilis; they observed subjective improvement in ten patients and increased range of motion in all patients. Brown and others (1951) reported their observations after treating eight patients with malum coxae senilis; two were improved, while six obtained neither subjective nor objective benefit. Thorn and others (1951) described alleviation of symptoms in a patient treated with ACTH who had generalized degenerative joint disease with involvement of both hips. Dale (1950a, b) reported treating two cases of osteo-arthritis who experienced dramatic relief of symptoms. These published reports suggest the need of a controlled study in the therapeutic evaluation of this condition.

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Material

Ten patients (see Table) were selected who had definite clinical amd roentgenographic evidence of the disease and showed objective evidence of limited mobility of the hip joint. The ten patients comprised five men and five women (nine white and one Negro), and their age ranged from 48 to 76 years. One hip only was involved in six cases, and both hips in the other four. Pain referable to one or both hips had been present for 1 to 5 years in 50 per cent. of the patients, and for 6 to 32 years in the other 50 per cent.

TABLE

RESULTS OF TREATMENT IN TEN PATIENTS

Patient	Age	Sex	Duration of Complaint (yrs)	Hips Involved	Range of Motion of Involved Hip (degrees)						Subjective Improvement	
					Placebo			Cortisone				
					Before	After	Flexion Change	Before	After	Flexion Change	Placebo	Cortisone
S.S.	76	M	15	Both	130-170	136-171	− 6	130-170	123-175	+ 7	Yes	Yes
A.L.	59	M	5	One	97-180	85-180	+12	85-180	85-180	0	No	Yes
P.S.	58	F	6	One	140-180	124-180	+16	124-180	135-180	−11	Yes	Yes
C.L.	60	F	27	Both	115-180	113-180	+ 2	113-180	110-180	+ 3	Yes	Yes
H.W.	71	F	6	One	85-180	80-180	+ 5	90-180	80-180	+10	No	Yes
E.F.	43	M	2	Both	85-180	85-180	0	85-180	95-180	−10	No	Yes
B.K.	48	F	3	One	70-180	100-180	−30	100-180	85-180	+15	Yes	No
J.D.	69	M	4	One	83-175	83-175	− 2	85-178	90-178	− 5	Yes	Yes
J.J.	63	M	3	One	120-180	110-180	+10	115-180	120-180	+ 5	No	No
L.L.	64	F	6	Both	145-170	123-175	+20	125-175	115-175	+10	Yes	Yes

Procedure

Before therapy was begun a red blood count, haemoglobin test, white blood count, differential, sedimentation rate, haematocrit, and urine analysis were undertaken. A complete physical examination was made, including roentgenograms of the hips and chest. The mobility of each hip was measured before and at weekly intervals during the study.

All patients were started on a placebo preparation which was continued for 22 days; this consisted of a raspberry syrup and potato starch mixture containing a very small amount of quinine which imparted the bitter taste simulating the cortisone solution. After completion of the placebo therapy, a cortisone preparation (25 mg. per 5·0 ml.) was started on all patients and continued for 22 days; this, too, was dispensed in a raspberry syrup and potato starch mixture. The cortisone was used in a dosage known to give relief to patients with rheumatoid arthritis, namely, 300 mg. the first day in divided doses 6-hourly, 200 mg. the second day, and 100 mg. thereafter for 20 days. All the patients except one were unaware of the nature of the drug used in the study.

All patients were studied as out-patients and seen at regular weekly intervals. At each visit the hip joint was measured for mobility, objective observations were made for any other increased function of the involved joint, and subjective responses were also noted, all measurements and observations being made by the same individual during the entire study.

Representative Case Histories

Case 1, J.D., 69-year-old white male, with a history of a painful and disabling right hip of 5 years' duration and without any known cause. His general health was good. He was able to flex the hip to an angle of 83° with the trunk, but found it difficult to cross the right leg over the left or to tie the lace of his right shoe. He was unable to continue

his work as a school watchman because of the walking and stair climbing. Roentgenograms of the right hip revealed a narrowed joint space, sub-cortical cystic areas in both ilium and femoral head, and sclerosis of the adjacent margins of the acetabulum. While receiving the placebo therapy the patient stated that he felt better and experienced a sensation of warmth over the right thigh. Objectively, the joint mobility remained the same. While receiving cortisone he continued to have less pain, but failed to demonstrate any increased mobility of the joint. Since both the subjective and the objective responses to the placebo and to cortisone therapy were essentially the same, the final result was considered negative.

Case 2, J.J., 63-year-old white male, complained of a painful right hip with inability to cross the right leg over the left or tie the laces of his right shoe. The condition was of 3 years' duration and had no known cause. His general health was good. Flexion of the right hip was measured at 120° with the trunk. Roentgenograms revealed marked narrowing of the joint space of the right hip, flattening of the femoral head, and sclerosis of the acetabulum. No subjective improvement was noted during either placebo or cortisone treatment. A 10° increase in flexion was noted while the patient was receiving the placebo, but no objective improvement was seen while he was on cortisone.

Case 3, L.L., 64-year-old white female, gave a history of having had a fall 5 years previously and having noted the onset of pain in the left hip several months later. The condition progressed and one year later caused the patient to stop working. Her general health was good. Roentgenograms revealed changes typical of severe degenerative joint disease of both hips. The right hip flexed to 145°. Shortly after the placebo therapy was started the patient said she had less pain and showed increased flexion of the right hip to 125°. While she was receiving cortisone, partial relief of pain continued and further increase in flexion of the right hip to 115° was noted. Even after cortisone was discontinued the subjective improvement of less pain and increased agility continued.

Results

The response in the remaining seven patients was similar to the three cases described above. Out of the total of ten patients, six showed subjective improvement during the control period and eight during the cortisone period. Subjective improvement consisted of a sense of well-being or euphoria, less pain, less stiffness, a feeling of ease in walking, etc. Objective response (see Table) consisted of increased mobility of the joint as measured with a goniometer.

During the control period the objective changes in the joint motion of the ten patients studied varied from decreases of as much as 30° to increases of as much as 20°. The increase in joint motion in five patients varied between 2° and 16°, and one patient showed an increase of 20°; three patients showed decreases of 2°, 6°, and 30° respectively; one showed no objective change at all.

During the cortisone treatment period increases in joint motion were seen in six patients, and varied from 5° to 15°; three patients showed a decreased motion of 5°, 10° and 11° respectively; one patient showed no objective change at all.

It should be noted that the increases and decreases in joint mobility observed during both the control and cortisone treatment periods were not appreciably different. The increases are probably not clinically significant, for increases of the extent observed are not infrequently seen and may probably be attributed to daily variations in the patient, plus errors of measurement used including the personal error of the observer. The greatest increase, one of 20°, was observed during the control period, but otherwise all the increases were essentially the same. The fact that the patients did equally well while receiving the placebo may represent

increased effort to help themselves such as is often observed when any new therapy is instituted.

In brief, the Table shows that six patients noted subjective improvement while on the placebo as compared with eight patients while on cortisone. Subjective improvement was usually of greater degree in the cortisone-treated patients. Objectively, the increases in mobility noted in the ten patients during both placebo and cortisone periods were essentially the same. On critical analysis, the objective improvement noted during the placebo period was slightly greater than that observed during the cortisone period. This may be explained by the fact that the placebo was the first form of treatment tried.

Comment

Medical treatment of malum coxae senilis has in the past been unsatisfactory. Recently the discovery of cortisone and our increasing knowledge of the physiology of the connective tissue has thrown some light on the mechanism and probable aetiology of the various collagen diseases and of rheumatoid arthritis in particular. In rheumatoid arthritis the use of cortisone is often followed by dramatic results, and although the pathology of degenerative joint disease differs from that of rheumatoid arthritis the clinical use of cortisone in malum coxae senilis seemed worthy of trial.

The results of this study of a small number of cases indicate that in degenerative joint disease of the hips the objective improvement manifested by increased motion of the joint is essentially the same after cortisone treatment as after when a placebo is used. The failure to obtain significant improvement in motion might be explained by the presence of irreversible intra-articular and peri-articular pathologic processes.

Although the cause of pain in this condition is unknown, it is of interest to note that eight of the ten cortisone-treated patients experienced partial relief of pain and noted other subjective signs of improvement, whereas during the control period a decrease in pain and subjective improvement was noted in only six of the ten patients. The mechanism of pain relief are unknown; an anaesthetic effect has been claimed for some of the steroids (Selye, 1941), and Grokoest and associates (1951) feel that relief of pain in rheumatoid arthritis and similar diseases evolves from a suppression of the inflammatory reaction in the host and not from a central or peripheral analgesic effect. Then, too, the subjective response may be related to the sense of well-being or euphoria seen in some patients receiving cortisone. The relief of pain obtained on administration of cortisone was greater than that obtained by the same ten patients during the control period. However, the pain relief and increase in joint motion when present in no case approached the dramatic levels of improvement seen in many patients with rheumatoid arthritis. The use of the same patients as controls also made clear the subjective and objective results which may appear during the administration of a placebo. The improvement noted during the control period tends to detract from the clinical benefit obtained from cortisone, but does not necessarily invalidate these results. The subjective responses, although incapable of measurement were significantly greater in the cortisone-treated patients than in the same patients when treated with the

placebo. It is clear that partial relief of pain without a clinically significant increase in the mobility of the involved hip is seen in cases of malum coxae senilis treated with cortisone.

Summary

(1) Ten patients with malum coxae senilis received first a placebo and later oral cortisone.

(2) Partial relief of pain was noted in eight of the ten patients while receiving cortisone, and in six of the ten patients while receiving the placebo.

(3) No clinically significant objective increase in mobility of the joint could be attributed to the use of cortisone.

(4) No untoward symptoms or reactions to cortisone were noted.

(5) The routine use of cortisone in malum coxae senilis cannot be recommended in view of the small improvement observed in the ten patients studied.

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La cortisone dans le traitement de la dégénérescence articulaire de la hanche

Résumé

(1) Dix malades atteints de coxalgie sénile reçurent par voie buccale d'abord une substance inerte et plus tard de la cortisone.

(2) Un allègement partiel de la douleur fut noté chez 8 d'entre eux lors de l'administration de la cortisone et chez 6 lors de l'administration de la substance inerte.

(3) On n'observa aucune augmentation cliniquement signifiante de la motilité articulaire attribuable à la cortisone.

(4) On ne nota pas de symptômes ou de réactions néfastes dus à la cortisone.

(5) En raison de la faible amélioration chez les dix malades étudiés, l'emploi régulier de la cortisone dans la coxalgie sénile n'est pas recommandé.

La cortisona en el tratamiento de la enfermedad degenerativa de la articulación coxo-femoral

Sumario

(1) Diez enfermos con coxalgia senil recibieron por vía oral primero una substancia de control y luego cortisona.

(2) Un alivio parcial del dolor fué observado en ocho de ellos durante la administración de la cortisona y en seis durante la administración del producto inerte.

(3) No se vió aumentación clínicamente significante de la movilidad articular que se pudiera atribuir a la cortisona.

(4) No se notó síntomas o reacciones desfavorables debidos a la cortisona.

(5) Por ser poca la mejoría en los diez enfermos estudiados, el empleo regular de la cortisona en la coxalgia senil no se recomenda.

COLSTON RESEARCH SOCIETY

SYMPOSIUM ON THE SUPRA-RENAL CORTEX

This symposium, held at Bristol University from April 1 to 3, 1952, was mainly concerned with chemical and biochemical research only indirectly linked with clinical medicine, but certain items were of interest and importance to rheumatologists.

PROF. C. H. LI (*California*), PROF. F. G. YOUNG (*Cambridge*), and DR. C. J. O. R. MORRIS (*London*) discussed methods of potentiating and fractionating ACTH and its bio-assay. The active principle seemed to be a basic polypeptide. Prof. Young thought that there were probably at least two active principles, corresponding to the adrenal weight increasing and ascorbic acid depleting fractions. It was agreed that the bio-assay by ascorbic acid depletion fixed by WHO did not correlate with other methods, such as adrenal weight, thymus inhibition, cholesterol depletion, white-cell reduction in the thoracic duct, or eosinopenic responses. In the discussion Dr. E. B. Astwood (*Boston, Mass.*) pointed out that unhypophysectomized man might not react like a hypophysectomized animal. Crude ACTH contained in addition to pure corticotrophin, growth hormone, a fat-mobilizing principle and intermedin, the melanophore stimulating factor.

PROF. J. M. YOFFEY (*Bristol*) discussed the histology of the adrenal cortex and the evidence for the action of ACTH on the zona reticularis.

PROF. F. VERZAR (*Basel*) appealed for the interrelationing and unification of the cortical hormones. He drew attention to the production of oxysteroids on perfusion of the adrenal with DOCA, and to the fact that this hormone can maintain secondary sex functions in adrenalectomized animals. He also stated that small repeated doses of gluco-corticoids had the electrolytic effects associated with DOCA. Gluco-corticoids affected the mobilization of glucose in the cell, from glycogen, fat, or protein, with subsequent deposition of glycogen. The potassium changes were secondary to these changes. Dr. H. Hoagland (*Shrewsbury, Mass.*) had isolated eight adrenal steroids after ACTH administration. Corticosterone and 17-hydroxy corticosterone made up the bulk, but about 3 per cent. cortisone and 2 per cent. desoxycorticosterone were also obtained. It was agreed that a considerable interconvertibility of the adrenal cortical hormones existed, but many who took part in the discussion were not prepared to believe in the complete overlap of gluco- and mineralocorticoids and sex hormones suggested by Prof. Verzar; it was asked, for instance, why a small dose of cortisone was so essential to the satisfactory control of a difficult case of Addison's disease.

DR. M. VOGT (*Edinburgh*) discussed the mechanism of stimulation of the anterior pituitary by adrenaline, stress reduction of corticoids, and stimulation of the hypophysis, and also the mechanism of direct stimulation of the adrenal cortex.

PROF. S. ZUCKERMAN (*Birmingham*) drew attention to the need for biological rather than chemical criteria in endocrinology, and to the danger of disarticulation of minutiae, as their interaction was so complicated. For instance, he suggested that both cortisone and sex hormones could be produced by the adrenal cortex and gonads on stimulation either by ACTH or by gonado-trophin. Dr. S. J. Folley (*Reading*), discussing lactation, mentioned work done with DOCA and cortisone implants. He thought one of the fundamental effects of the gluco-corticoids was on glucogenesis from the fatty acids. Dr. F. T. G. Prunty (*St. Thomas's Hospital, London*) also emphasized the need to integrate chemical and biochemical observations; he illustrated his point by quoting such complicating factors as the synergic effects of luteinizing hormone and cortisone, and the apparent difficulty in interpreting ACTH potency by ascorbic acid depletion when scorbutic guinea-pigs react very well to ACTH.

PROF. G. F. MARRIAN (*Edinburgh*) summarized his present work. Formaldehydogenic steroid is lost on allowing acid urine to stand and in extraction at *p*H I., glucuronidase hydrolysis increased the yield seven- or eight-fold. The method was not yet, however, properly standardized, and the hydrolysis did not affect a conjugated fraction, and was not yet, therefore, a method suitable for routine application.

DR. H. J. ROBINSON (from Messrs. Merck Ltd., U.S.A.) showed that with large doses of cortisone or ACTH (5 mg. daily) in rabbits, pneumococcal lesions were increased in size, and the leucocyte reaction in the tissues, ingestion of bacteria, and immunity titre were all delayed with increase in mortality. With small doses (0·5 mg. daily or less), however, the treated group reacted better than the controls. Cortisone had little effect on toxins, but did not reduce the lethal dose of pyrogens. Dr. R. R. H. Lovell (*London*) said that in man the dose of cortisone necessary to reduce experimental skin inflammations was generally higher than that found effective therapeutically. Perhaps this was why dissemination of infection occurred less commonly than might be expected from animal experiments. Dr. M. Reiss (*Bristol*) drew attention to the importance of distinguishing the effects of small and large doses of these hormones, stating that many years ago he had found increased ingestion of carmine by the reticulo-endothelial system during treatment with small doses of crude ACTH—the opposite effect to that obtained with present-day large doses.

DR. H. HOAGLAND (*Shrewsbury, Mass.*), and DRS R. E. HEMPHILL and M. REISS (*Bristol*) then discussed the effects and abnormalities of hormones in mental disease. Among other matters, the high and irregular ketosteroid excretion, poor reaction to stress, and clinical deterioration with hyper-adrenalism in schizophrenia was agreed; whether these results occurred *post hoc* or *propter hoc* was uncertain, but in the United States adrenalectomy had been tried as a method of treatment. In psychosis, E.C.T., insulin, testosterone, and ACTH treatment often had considerable value, but their effect was complicated. Hyperthyroidism was a brake on the reaction of ACTH.

PROF. G. R. CAMERON (*University College Hospital, London*) described possible changes in the tissues resulting from the use of ACTH and cortisone, and the inhibition of the hyaluronidase spreading effect, the histamine and leucotactic polypeptide reaction, and the diffusion of fluorescein from the blood vessel of the eye. Delayed healing was also demonstrated, but it was the speed and amount of repair that was altered and not the general pattern. The question of inhibition of cell mitosis is still uncertain.

DR. P. L. KROHN (*Birmingham*) then discussed the effect of cortisone in controlling the inflammatory reaction which prevents homogeneous skin grafts from taking; again the reaction is delayed not altered, the grafts eventually succumbing. Dr. O. A. Trowell (*Harwell*) showed a delayed toxic effect of cortisone on lymphocytes *in vitro*; there was no effect on macrophages. Prof. J. M. Yoffey demonstrated an absolute increase in erythroid and myeloid cells in the bone marrow with ACTH; there was little if any change in the absolute number of lymphocytes in the marrow. Dr. K. Aterman described experiments suggesting an effect of cortisone on well-formed fibrous tissue, but this was challenged by other workers.

DR. DWIGHT J. INGLE (from the Upjohn Coy., U.S.A.) discussed the synergic effect of oestrogens and cortisone in the production of diabetes and control of hair growth in rats. With regard to "stress" and "diseases of adaption" he felt that stimulation of the adrenals was a defence mechanism which did not constitute hyper-corticism, but might contribute to the symptomatology of disease without actually causing it.

PROF. H. HELLER (*Bristol*) outlined the influence of the adrenal cortex on mineral and water metabolism.

MR. L. R. BROSTER (*Charing Cross Hospital, London*) described clinical varieties of virilism and the correlation between the degree of virilism and the degree of fuchsin staining of the adrenal. Dr. Jolley emphasized the value of cortisone in treating congenital adrenal hyperplasia, especially if the treatment was started early. Dr. Hoagland mentioned the very satisfactory results of total adrenalectomy+orchidectomy in carcinoma of the breast and prostate.

DR. E. B. ASTWOOD (*Boston, Mass.*) described the action of cortisone and ACTH as anti-allergic or anti-phlogistic. Hydro-cortisone was said to be slightly more active than cortisone both clinically and in its "electrolytic" effects, and was best used locally or orally, since intramuscular injections were absorbed very slowly. Local treatment could be used for the eye, for joints, and as an aerosol for asthma. A much purified preparation of ACTH had been produced which used intramuscularly was much more potent clinically than was suggested by assay or might be expected from its concentration. Intravenously, however, this enhanced potency was much less spectacular. Considerable progress had been made in delaying the absorption of ACTH by administering it in an oil or gelatin base.

DR. G. D. KERSLEY (*Bath*) urged that each patient should be considered on his own merits, remembering the temporary blanketing effect on allergy and fibrosis. These principles must be applied after consideration of the patient's history, the stage of the disease, other complications, and the social background, since both hyperergy and scarring could be either helpful or harmful. In rheumatic fever the value of these hormones was doubtful, in spondylitis they vied with radiotherapy in the treatment of young women only, and in rheumatoid arthritis they were very helpful in the short-term treatment of acute attacks due to a temporary cause, to cover rehabilitation, in manipulation, and sometimes with surgery. He then described two cases of rheumatoid arthritis clinically resistant to 400 mg. ACTH daily and 100 mg. intravenously, and one who failed to react to 500 mg. intramuscular cortisone daily or 50 mg. intra-articular hydro-cortisone. Finally, he pleaded for a balanced view of the value of cortisone. In the discussion, Dr. P. Ellman (*London*) described a case of Addison's disease with rheumatoid arthritis well controlled with 1·5 mg. DOCA and 25 mg. cortisone daily. Dr. West mentioned a patient with a duodenal ulcer which healed while he was receiving cortisone, and another patient who developed severe amyloid disease. Dr. J. J. R. Duthie (*Edinburgh*) drew attention to the absence of any correlation between the severity of the disease and the therapeutic dosage of cortisone. He also said the results of cortisone and intravenous iron therapy combined in rheumatoid arthritis were good in that the red-cell count increased.

HEBERDEN SOCIETY

Clinical Meeting.—Prof. Sir Henry Cohen, the President, took the chair at a clinical meeting held at the London Hospital on February 29, 1952.

MR. OSMOND-CLARKE demonstrated two patients on whose hips arthroplasties had been performed. The operation was of the Judet type with excision of the femoral head and replacement by an acrylic one. Both patients had almost complete relief of pain and their mobility was impressive. Mr. Osmond-Clarke pointed out that if the operation was performed before there was gross change in the joint a range of movement approximating to normal could sometimes be obtained, but if gross changes were present in the acetabulum the range of movement was not so satisfactory.

SIR RUSSELL BRAIN demonstrated a case of cervical spondylosis. A market porter, aged 58, 2 years previously, while carrying a sack of potatoes on his head up a ladder, had felt " something click " in his neck and had severe pain in the neck and right shoulder. For 6 months before admission he had weakness in his arms and legs, and for 2 months had been unable to work. He had tingling in the finger tips of both hands and increasing pain in the neck. On examination there was wasting of the arms and hands with inverted radial reflexes, and spastic weakness in the lower limbs with extensor responses. There was no definite sensory loss in either upper or lower limbs. X ray showed cervical spondylosis between the 4-5 and 5-6 cervical vertebrae.

SIR HORACE EVANS showed a case of rheumatoid arthritis (Still's disease) with amyloidosis. A female, aged 28, had a history of 12 years' progressive polyarthritis complicated by pneumonia, meningitis, and pericarditis. On the present admission she was febrile with oedema and ascites in addition to arthritis. Investigations showed evidence of renal and liver damage. The blood sedimentation rate was 60, with reversed albumin/globulin ratio, and amyloid infiltration was shown by liver biopsy. Treatment with cortisone for 7 weeks improved the polyarthritis considerably, but had no effect on the albuminuria, liver function tests, or liver histology.

DR. J. O. STOREY showed a case for discussion. A gas-fitter, aged 33, with a history of attacks of pain in the shoulders, had attacks of peripheral joint swellings with a raised erythrocyte sedimentation rate, and had recently developed abnormal neurological signs in the upper limbs.

Sixty members of the Society were present and a discussion followed the presentation of each case.

Heberden Round.—This was conducted by the President of the Society, Professor Sir Henry Cohen, at the Royal Infirmary, Liverpool, on April 18, 1952. A large proportion of members gathered for this demonstration, at which Sir Henry showed a variety of cases of the diffuse collagen diseases which had been under treatment with cortisone and ACTH.

Disseminated Lupus Erythematosus.—Four cases were shown, each exhibiting different grades of skin and visceral involvement, varying from dermatitis with minimal constitutional change, to a case with slight rash and multiple involvement of serous membranes. There had been general improvement with ACTH, but in at least one case the histology had remained unchanged. One patient was being maintained in good clinical condition by a small dose of hormone given every 5 days, but any attempt to omit this resulted in a relapse.

Dermatomyositis.—A child was shown who was also being maintained on a small amount of ACTH given every few days. Attempts to substitute cortisone to avoid injections had resulted in a rapid relapse.

Scleroderma.—An advanced case had failed to respond to intravenous ACTH.

Sjögren's Syndrome.—A woman patient whose symptoms included swollen and painful parotid glands, granulopenia, arthritis, and hepatitis had responded satisfactorily to ACTH and there was evidence of improvement in hepatic function.

Temporal Arteritis.—In one case proved by biopsy there had been relief of bilateral intense headache coincident with the exhibition of ACTH.

Pemphigus Vulgaris and **Simmond's Disease.**—Cases were shown in which a response to adrenocorticotropic hormone had been observed.

A feature of this excellent demonstration was the small dosage of the hormone which had been found necessary to maintain clinical improvement in some of those cases which had responded to therapy.

Sir Henry Cohen afterwards entertained the members of the Society to dinner at the Staff House of the University of Liverpool.

EMPIRE RHEUMATISM COUNCIL

FIFTEENTH ANNUAL REPORT

The fifteenth annual report of the Empire Rheumatism Council was presented by the Chairman, Lord Horder, at the Annual General Meeting held on April 29, 1952, in the historic precincts of St. James's Palace by gracious permission of His late Majesty King George. He recorded their deep sorrow at the passing of a Ruler whose devotion to duty and singleness of purpose would remain for all time an example and an inspiration. He offered to the President and to the Members of the Royal Family deep sympathy in the grievous loss which they and the Empire had sustained.

Having expressed the grateful thanks of the Council to the President for his continued interest, to the members of the various committees for their voluntary services, and to the Honorary Medical Secretary for his periodic Reports to the Executive and Scientific Co-ordinating Committees, the Chairman drew attention to the change in the status of the Council effected by its incorporation in January, 1951.

The incorporation of the Council had given an opportunity to bring into close collaboration at the Annual General Meetings many of the donors and subscribers who might like to be associated personally with members at least once a year. Accordingly, the Executive Committee, on the recommendation of their *ad hoc* committee, had decided upon the following qualifications for Membership:

(*a*) that donors of £1,000 or over should be invited to accept a " Vice-Presidency " of the Council,

(*b*) that donors of £100, or of an equivalent amount under Deed of Covenant, should be invited, as at present, to accept a " Life Councillorship ",

(*c*) that all other Deed of Covenant subscribers and donors of a sum of three guineas or over per annum should be invited to accept Membership for the year or years covered by their subscription or donation.

These decisions did not exclude others who, apart from financial considerations, had rendered distinguished service to the Council in a medical or advisory capacity.

Research.—At the hospital of St. John and St. Elizabeth, research on the metabolic effects of various steroid hormones and related substances in rheumatoid arthritis was carried on by Dr. A. A. Henly, and his assistant, Miss M. I. Potter. Much useful biochemical information had been obtained during clinical trials of ACTH and cortisone. A number of possible cortisone substitutes had been investigated but with disappointing clinical results. These studies were being continued, using improved analytical methods developed for that purpose.

The Clinical Trials Group of which these studies formed part was centred in the Rheumatism Department of the West London Hospital; it included, in addition to Dr. W. S. C. Copeman and Dr. O. Savage, Prof. E. C. Dodds, F.R.S., Dr. Peter Bishop, and Dr. J. Moore Tweed (Philip Gray Fellow).

Dr. Billimoria, who was working on the development of new compounds under the supervision of Prof. Maclagan and with the clinical collaboration of Dr. F. Dudley Hart at the Westminster Hospital Medical School, had submitted a progress report with a programme of future work. He had prepared a number of new compounds resembling parts of the cortisone molecule, but of considerably smaller molecular size. These were being tested both by biological methods and by clinical trials, and it was hoped that some might possess useful anti-rheumatic activity. This work was also of some possible importance as a model for synthetic routes to cortisone itself, an aspect which had been recognized by the National Research Development Corporation who had taken out a patent on one of the processes employed.

The two Elizabeth Macadam Fellows, Dr. G. Loewi, working at the Canadian Red Cross Memorial Hospital, Taplow, under the direction of Dr. E. G. L. Bywaters, and Dr. J. L. Potter, working at the Northern General Hospital, Edinburgh, under the supervision of Dr. J. J. R. Duthie, had continued their investigations into the aetiology and pathogenesis of ankylosing spondylitis. Dr. Loewi examined ligaments and connective tissues from the spine and elsewhere, using a combination of biochemical and histological techniques. An abnormally high polysaccharide content was found in some of the specimens, and might play a part in subsequent calcification. Dr. Potter had been studying the effects of radiotherapy; it would appear that its beneficial effects in ankylosing spondylitis might depend partly on stimulation of the adrenal gland.

A further research fellowship to be known as the Philip Gray Fellowship (now held by Dr. J. Moore Tweed) had been made possible by a generous contribution from the Shell Petroleum Company in memory of the late Mr. A. P. Gray, a sufferer from rheumatoid arthritis.

The Council had continued to assist the investigations of Mr. A. J. Whiten, F.R.Met.S., into the effects of climate in rheumatism, with the statistical help of Dr. Lewis-Faning. It was possible that a more ambitious programme of research might be undertaken at the R.A.F. Institute of Aviation Medicine at Farnborough, or at Dr. G. Edström's Unit in Sweden.

A sub-committee appointed to make a trial of adrenaline cream had published their adverse findings in the *Annals of the Rheumatic Diseases*, and a summary had appeared in the *Lancet* and the *British Medical Journal*.

Grants for equipment and apparatus for hormonal research had been made to many centres, including University College Hospital, and Royal Free Hospital, London; Royal Mineral Water Hospital, Bath; Royal Infirmary, Manchester; Northern General Hospital, Edinburgh; and Canadian Red Cross Memorial Hospital, Taplow.

Following the publication of the *Report on the Chronic Rheumatic Diseases* issued by the Royal College of Physicians, the Council had convened a Regional Sub-committee to discuss problems relating to rheumatic research, treatment, and education; to exchange information; and to consider matters wherein the Empire Rheumatism Council could be of assistance. Information was to be presented from the Regional Hospital Board areas regarding treatment, research, and education; staff available (including Registrars); inter-relationship with physical medicine; and other regional problems. This sub-committee should thus assist in improving existing facilities and initiating schemes to forward the suggestions made in the Report.

The British Branch of the European League against Rheumatism had continued to receive financial aid from the Council. The European Congress on Rheumatology, organized at Barcelona by the Spanish Rheumatism Society under the auspices of the European League against Rheumatism, had been one of the outstanding gatherings of 1951.

Education.—The Education Sub-committee felt that it could serve a useful purpose in bringing to the notice of the Royal College of Physicians the deficiency in education of students and practitioners, and in submitting evidence of progress to the Regional Medical Boards.

Post-graduate lecture and demonstration courses had been held by permission of the Middlesex Hospital, at the Arthur Stanley Institute, Peto Place.

Of a series of broadcast talks, published by the Council during 1950, over 13,000 copies had been sold. The copyright had been generously presented by the author to the New Zealand Rheumatism Council and the Australian Rheumatism Council, both of which had received copies for advance distribution, and similar facilities had been accepted by the Canadian Arthritis and Rheumatism Society.

The first issues of the *Annotated Bibliography of Cortisone, ACTH, and Related Hormonal Substances* had appeared in December, 1950, and April, 1951. The Council was indebted to Dr. Oswald Savage for his meticulous care in preparing them.

Commonwealth.—The first meeting of the Commonwealth Sub-committee had been held in February, 1951. Its functions were agreed to be education and published literature; and the interchange of fellowships and scholarships between the United Kingdom and the Commonwealth, thus placing research workers in the most advantageous positions.

The second Annual Report (1949-50) of the Canadian Arthritis and Rheumatism Society had recorded a successful year of progress, an outstanding item being the award of eleven Fellowships tenable in Canada, America, and England. Three Fellows had been appointed to England—two to the West London Hospital, and the third to the Royal Infirmary, Manchester. This exchange of personnel afforded a valuable opportunity of gaining experience of the systems in operation in other countries.

The first Annual Report (1949-50) of the Australian Rheumatism Council showed that they too were forging ahead.

Finally, the Chairman said that as the Empire Rheumatism Council was free from state control and was not state-aided, an opportunity presented itself to all charitably disposed persons to devote their financial assistance to furthering the Council's medical and scientific research into one of the most prevalent, prolonged, and painful disorders afflicting mankind.

LIGUE EUROPÉENNE CONTRE LE RHUMATISME

THIRD EUROPEAN CONGRESS, 1955

The third congress of the European League against Rheumatism will be held in Amsterdam in the spring of 1955, probably at the end of April or beginning of May (the flowering-time of the bulbs). Members of the Dutch Branch of the European League (Nederlandske Vereniging van Rheumatologen) will act as hosts and organizers of the congress.

NOTE

A course of 24 lectures on aspects of rheumatic disease was given in April and May, 1952, at the Rheumatism Clinic of the Hospital de la Santa Cruz y San Pablo, Barcelona, under the direction of Dr. José M. Poal.

INTERNATIONAL CONGRESS OF PHYSICAL MEDICINE, 1952

This Congress will be held from July 14 to 18. The headquarters will be King's College, London. The following items from the programme will be of special interest to rheumatologists.

July 14 (*Afternoon*): Opening of Scientific and Historical Exhibition by the President, Lord Horder.

July 16: Symposium on Rehabilitation and Resettlement. Films of interest to rheumatologists.

July 17 (*Morning*): Symposium on Management of the Chronic Rheumatic Patient, and on Other Disorders of the Locomotor System. Prof. Sir Henry Cohen will speak on "The Endocrines in the Management of Chronic Rheumatic Disorders", Prof. L. Michotte on "Douleurs du dos", and Drs J. B. Burt, E. Fletcher, D. A. Kininmonth, and S. Mattingly on "Painful Shoulder". The Brains Trust will comprise Sir Henry Cohen, and Drs J. B. Burt, F. D. Howitt, W. Tegner, K. M. Walthard, and Prof. L. Michotte. (*Afternoon*): Further papers on the rheumatic diseases. Dr. H. Petty will speak on "Orthopaedic Aspects of Rheumatoid Arthritis", Dr. F. S. Bach on "Cortisone and Physical Treatment in Rheumatism", Dr. W. A. Fell on "Treatment of Osteo-Arthritis by Procaine Injection", Prof. J. Michez on "Physiotherapy in Rheumatoid Arthritis", Dr. E. W. Lowman on "Rehabilitation of the Rheumatoid Derelict", Dr. J. M. Poal on "Traction of Cervical Spine in Osteo-Arthritis", Dr. A. Stoddard on "Short Leg and Low Back Ache", and Dr. W. D. Paul on "Permeability of Synovial Membrane".

Further particulars may be obtained from the Honorary Secretary, Dr. A. C. Boyle, 45 Lincoln's Inn Fields, London, W.C.2.

HOSPITAL REPORTS

That important work is being done in many hospitals in London and throughout Great Britain may be gathered from the publication in the *Annals* of the results of researches in these centres. In these days costs limit publicity, but if the hospitals could bring this need to the notice of their supporters and benefactors of the days before the National Health Service took over, it is likely that private benevolence might be attracted to assist. The munificent support of the Nuffield Trustees must be recognized and appreciated, especially in the Unit established in connection with the University of Manchester. The Empire Rheumatism Council does important work in organizing and endowing research, and other sources of benevolence might be quoted.

Research into the use of cortisone and ACTH has been a notable feature at the Rheumatism Department of the West London Hospital, which has issued an interesting Report, part of the cost having been defrayed by the Trustees of the Dan Mason Research Foundation.

For the fourth year in succession the Royal National Hospital for Rheumatic Diseases, Bath, has presented a Report of the investigations carried out by members of the staff and other research workers. Clinical studies of hydrotherapeutic treatment in rheumatic diseases would be of value from this hospital which has facilities lacking in many research centres.

The Department of Rheumatism of the Royal Free Hospital, London, has also presented its fourth Annual Report, in which extensive statistics, in the preparation of which the assistance of Dr. Lewis-Faning is acknowledged, are a valuable feature. As in the past, rehabilitation and resettlement are receiving special attention; this work, though often difficult and sometimes disappointing, is well worth while.

Restrictions in the size of the *Annals of Rheumatic Diseases* for reasons of expense prevent a more comprehensive review, but copies of these Reports could be obtained on application to the appropriate physician in charge. It is hoped that in future reports of the work being done in many other centres will be made public.

BOOK REVIEWS

First Annual Report on Stress. By Professor Hans Selye. 1951. Pp. 511, approx. 3,000 refs. Acta Inc., Montreal. ($10, 80*s.*)

In this volume Professor Selye has given us yet another proof of his remarkable qualities. By a feat of superb organization he has collected over 3,000 publications relevant to his subject which appeared during 1951. These have been classified, extracted, and incorporated into something which is part review, part medical index. The format is original and it is essential to read the preliminary chapter which explains how the volume should be used.

In the concept of stress and the diseases of adaptation, the pituitary growth hormone (STH) now figures prominently as a supporter of the mineralo-corticoids (M-Cs) against ACTH and the gluco-corticoids (G-Cs) in the endocrine balance, and with variations in target responsiveness and the participation of other organs the concept becomes one of considerable complexity which can be adapted to fit most contingencies. Bodily and enzyme systems, metabolic processes, and disease entities are dealt with in detail in the various chapters; the clear subheadings and the arrangement whereby references appear in brief at the bottom of each page allow one to pick out those relevant to any particular subject in a minute or two. Thus this volume should be invaluable as a source of reference.

Each of the special chapters contains some masterly logical exposition, of which the following is a typical example:

> It is specially important to keep in mind that the "Diseases of Adaptation" theory of rheumatoid arthritis does not necessarily presuppose an absolute increase in M–C production, but merely an increased M–C activity. The latter may result (*a*) from an absolute increase in M–C production, (*b*) from a relative decrease in G–C production with a consequent rise of the M–C/G–C ratio, (*c*) even in the absence of any change in corticoid output, increased M–C activity can result, through changes in metabolism which specifically sensitize or "condition" the tissues to M–Cs (e.g. increased STH production, Na retention).

I have quoted at length to illustrate the real quality of the writing, which is not easily described. The author's experiments upon rats are continually brought in to illustrate these arguments which form the main material of the book.

In the introduction, where the author is expounding his "scientific credo" with one of the diagrams with which this book is freely illustrated, he says "examine your own and *all* other pertinent data critically" and then "eliminate the untrue and unimportant". The interpretation of data may often be incorrect but it surely requires a special credo to classify data into "true" and "untrue".

J. H. KELLGREN.

Symposium on the Influence of the Hypophysis and the Adrenal Cortex on Biological Reactions. Held by the Swiss Academy of Medical Sciences under the auspices of the Council for the Co-ordination of International Congresses of Medical Science, World Health Organization, American-Swiss Foundation for Scientific Exchange, Inc., and CIBA Pharmaceutical Products, Inc. 1952. Benno Schwabe Verlag, Basel. Pp. 228, 75 illus., 28 tables. (16 Swiss Frs).

This is the published record of a symposium held in Zürich, from September 30 to October 2, 1951, under the auspices of the Swiss Academy of Medical Sciences. It provides a fairly complete summary of the influence of the hypophysis and the adrenal cortical glands on the physiological and pathological processes of the human body, so far as they have at present been determined. Many of the contributors are well known; amongst the British contingent were Prof. G. W. Pickering and Dr. D. A. Long (*London*), and Dr. P. H. G. Gell (*Birmingham*). Dr. R. Levine (*Chicago, Ill.*) opened the symposium with a survey of the functions of the adrenal cortex as a regulator in tissue reactions. Dr. G. Sala and his team from Milan spoke of their experimental studies with cortisone. The problem of the relationship of hyaluronidase to the aetiology and progress of collagen diseases, and the effect of cortisone on the tissue synthesis of acid mucopolysaccharides were dealt with by Drs J. Seifter (*Philadelphia, Pa.*) and L. L. Layton (*Baltimore, Md.*), and Drs C. Holten and K. Lundbaek (*Aarhus, Denmark*) read an interesting paper on metabolic and renal diabetes produced by the administration of ACTH.

Professor G. Miescher, the President of the Swiss Academy of Medical Sciences, who wrote the foreword (in English, French, and German), pointed out the need for basal research regarding the site of action of the adrenal steroids, and sounded the necessary warning that the results of experimental work performed on the lower animals were not necessarily applicable to man.

This is a useful presentation—largely in English—of a number of valuable reference papers not published elsewhere.

W. S. C. COPEMAN.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the three abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, ABSTRACTS OF WORLD SURGERY, OBSTETRICS AND GYNAECOLOGY, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism: Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous): Sciatica: Gout: Non-Articular Rheumatism: General Pathology: ACTH, Cortisone, and other Steroids: Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section " ACTH, Cortisone, and other Steroids " includes abstracts and titles of articles dealing with steroid research which, although not directly concerned with the rheumatic diseases, may make an important contribution to knowledge of the scope and *modus operandi* of steroid therapy.

Acute Rheumatism

Combination of Hormones and Salicylates in the Treatment of Acute Rheumatism. (Le traitement hormonosalicyle de la maladie de Bouillaud.) JANBON, M., BERTRAND, L., SALVAING, J., and LABAUGE, R. (1951). *Pr. méd.*, **59**, 1344. 4 figs, 19 refs.

The authors discuss the effects of ACTH and cortisone on rheumatic carditis and endocarditis and the lack of agreement on dosage—Coste advocating the use of a constant daily dosage (10 mg. ACTH or 120 mg. cortisone) for about 6 weeks, and Hench favouring larger doses for about 10 days followed by smaller ones. As the hormones are in short supply, the authors decided to use them for initial therapy only, thereafter continuing with salicylates. They consider that with this " coupled treatment ", as they call it, the worst side-effects of either remedy given by itself are avoided. Cortisone is preferred to ACTH and, in adults, they give 300 to 400 mg. on the first day (divided into four doses), 200 to 300 mg. on the second, and 100 to 200 mg. on the third and (sometimes) on the fourth; the total dosage is thus between 600 mg. and 1 g. cortisone. Without further treatment a relapse can be expected on the fifth day, and it is therefore important to start salicylate treatment without delay, the authors giving sodium gentisate by mouth (14 g. daily in several doses) and sodium salicylate by intravenous injection (4 g. daily in two doses). Details are given of eighteen patients treated, twelve of whom were in their first attack of rheumatic fever and six cases of relapse. It is claimed that this form of treatment is both efficacious and the most economical way of using the hormones in the treatment of rheumatic fever. [The original article should be consulted for clinical details.] *D. Preiskel.*

Systemic Arterial Embolism in Rheumatic Heart Disease. DALEY, R., MATTINGLY, T. W., HOLT, C. L., BLAND, E. F., and WHITE, P. D. (1951). *Amer. Heart J.*, **42**, 566. 4 figs, bibl.

The authors studied 194 patients with rheumatic heart disease diagnosed clinically or at necropsy (39 cases) during the years 1923-50. A mitral lesion was present in 188; auricular fibrillation, usually of some duration, but less often paroxysmal or of recent origin, occurred in 174 patients. There was little evidence that digitalis was a significant factor, and in only one of eleven patients treated with quinidine was embolism possibly due to restoration of normal rhythm. [Normal rhythm was not restored in the other cases.] Moderate rather than extreme left auricular enlargement was usually present. Cardiac failure, exercise, surgical operations, and pregnancy did not appear to be precipitating agents.

Intracardiac thrombi were present in 25 of the 39 cases coming to necropsy, and a probable site of origin was seen in six others. The thrombus was in the cavity of the left auricle in eleven, in the auricular appendage alone in ten, and in both in four cases. Active rheumatism was present in nine cases, in eight of which there was a visible thrombus.

Emboli to the number of 393 were observed in the 194 patients, who varied in age from 7 to 74 years: 48 per cent. were to the brain, 14 per cent. to the arteries of the abdominal viscera, 11 per cent. to the aortic bifurcation and iliac arteries, 17 per cent. to the arteries of the lower extremity, and 10 per cent. to the arteries of the upper extremity. Of the 194 patients, 71 per cent. are known to be dead: 12 per cent. from the initial embolus, 28 per cent. from subsequent emboli, and most of the remainder from cardiac failure. The highest mortality from all causes was in the first year after the initial embolus, but fatal emboli continued to occur 10 or more years later. Particularly dangerous sites were the cerebral vessels (64 deaths in 130 patients) and mesenteric arteries (ten deaths in eleven patients).

Early recognition, prompt embolectomy, and the use of anticoagulants are stressed as essential in cases with emboli to the aortic bifurcation and lower limbs. No treatment is considered to improve the prognosis of cerebral embolism. The prophylaxis of recurrent embolism is also discussed, including the continued use of anticoagulants over long periods, the avoidance of too rapid diuresis by digitalis or mersalyl, administration of quinidine, and amputation of the auricular appendage.

[This is an important paper which should be read in detail by all interested in this subject.] *J. W. Litchfield.*

Effect of Cortisone and Corticotropin (ACTH) on the Acute Phase of Rheumatic Fever. Further Observations. BARNES, A. R., SMITH, H. L., SLOCUMB, C. H., POLLEY, H. F., and HENCH, P. S. (1951). *Amer. J. Dis. Child.*, **82**, 397. 16 figs, 6 refs.

In studying the effect of any therapeutic agent in a self-limiting disease such as rheumatic fever it is important to note the point in the course of the disease at which the agent is administered, as the effect is likely to vary considerably at different stages. For the purpose of analysis of the effects of treatment with cortisone and ACTH the

authors' patients were therefore classified into the following categories:

(1) those with acute rheumatic fever in the first attack and without cardiac damage (eight cases);

(2) those with acute rheumatic fever in the first attack, but complicated by rheumatic carditis (two cases);

(3) those with a recurrent attack of rheumatic fever complicated by previous cardiac damage (four cases).

The authors found that the hormones suppressed the acute manifestations of rheumatic fever, but that until the disease had run its usual course exacerbations recurred when they were discontinued. To be most effective it seemed that the hormones should be given in adequate amounts early in the acute phase of the attack and administration continued in reduced amounts until the activity of the disease is at an end. The authors state that their experience in these cases gives rise to the hope that early adequate administration of these hormones in initial or subsequent attacks of rheumatic fever may prevent or minimize permanent cardiac damage in a majority of cases, although it will need several years of follow-up before it can be seen how fully this hope is justifiable. Only in one case had treatment to be discontinued owing to the occurrence of side-effects.

W. S. C. Copeman.

Anaemia of Rheumatic Fever. COCHRAN, J. B. (1951). *Brit. med. J.*, **2**, 637. 4 figs, 7 refs.

Anaemia, of sudden onset and at times severe, is a well-known feature of rheumatic fever. Previous studies have revealed no evidence of increased blood destruction. It was regarded as a fault in erythropoiesis, until Bradley in 1938 brought evidence to show that the apparent anaemia is only relative, resulting from increased plasma volume.

Further evidence that the anaemia is a dilution phenomenon is recorded in this paper. Estimations of the haemoglobin, haematocrit, and number of erythrocytes were made in ten patients with rheumatic fever; fluid balance studies were made in each case. In one patient, frequent plasma volume determinations were made, and the results plotted against the corresponding haemoglobin levels. The anaemia was found to be normocytic, normochromic, or slightly hypochromic. Repeated estimations throughout the course of the disease showed a close direct relationship between haemoglobin and packed cell volume; a rise in haemoglobin was associated with increase in fluid output over intake; and a striking inverse relationship was demonstrated between haemoglobin levels and plasma volume.

An inverse relationship was also shown between haemoglobin and erythrocyte sedimentation rate, the haemoglobin level serving as a good indication of rheumatic activity. The author suggests that hydraemia and changes in the osmotic pressure of the plasma may be important factors in this and other anaemias associated with infection.

Kenneth Stone.

Q-T Interval in Rheumatic Fever. BRIGGS, J. N., and DOXIADIS, S. A. (1951). *Arch. Dis. Childh.*, **26**, 311. 1 fig., 12 refs.

The author estimated QTc in 82 rheumatic children and twenty non-rheumatic controls. Taking 0·422 as the upper limit of normal, QTc was found to be prolonged in 12 per cent. of the recordings from rheumatic children and in none of those from the controls.

The rheumatic children were considered in three groups: those suffering from rheumatism with and without active carditis and those with inactive rheumatic heart disease. There was no clear difference in the frequency of prolonged QTc in these groups, so that QTc estimation is not a reliable guide to the diagnosis of active carditis. In an occasional case, however, diminution of QTc may be noted as the carditis subsides.

J. A. Cosh.

Prevention of Rheumatic Fever by Prompt Penicillin Therapy of Hemolytic Streptococcic Respiratory Infections. Progress Report. MASSELL, B. F., STURGIS, G. P., KNOBLOCH, J. D., STREETER, R. B., HALL, T. N., and NORCROSS, P. (1951). *J. Amer. med. Ass.*, **146**, 1469. 19 refs.

The study reported was based on 46 haemolytic streptococcal infections occurring in forty rheumatic subjects: 34 of the infections were treated with penicillin, the remaining twelve, " for various reasons " [unspecified] being untreated and therefore regarded as controls. Five of the patients were treated intramuscularly with aqueous benzyl penicillin in divided doses totalling 120,000 to 400,000 units per day. In the remaining patients penicillin was administered by the mouth in the form of buffered tablets of sodium or procaine benzyl penicillin, usually in doses of 1,000,000 units a day. The treatment in all cases was given as soon as possible after the infection started and was continued for 10 days.

Recurrence of the rheumatic fever developed during only two of the 34 penicillin-treated infections; in contrast there were six instances of recurrence following twelve untreated infections. The authors conclude that prompt penicillin therapy in streptococcal infections may reduce the incidence of rheumatic recurrences.

R. S. Illingworth.

Treatment of Acute Rheumatism with Cortisone and ACTH. (Traitement de la maladie de Bouillaud par la cortisone et l'ACTH.) COSTE, F., and OURY, M. (1951). *Pr. méd.*, **59**, 1493. 12 refs.

In this valuable article the authors give provisional answers, based on their own observations in 43 cases and the published experience of others, to a number of questions concerning the treatment of rheumatic fever with cortisone and ACTH.

It is stated that fever abates as a rule in 1 to 6 days, but the temperature may not become steady for 2 or 3 weeks. However, the initial fall in temperature is so constant as to be almost diagnostic. Tachycardia is more persistent, the pulse taking 1 to 3 weeks longer to become stabilized. Arthralgia quickly diminishes, but joint swelling is a little more tenacious. Nodules disappear in 3 to 4 weeks and the erythrocyte sedimentation rate (E.S.R.) becomes normal between the 10th and 31st days of treatment.

Pericardial friction usually disappears in less than a week, though regression of the cardio-pericardial *x*-ray shadow often takes 2 to 3 weeks. The effect on the endocarditic lesions depends essentially on the initial condition of the heart and on the duration of the acute phase before treatment is started, the authors never having observed regression of the signs of established rheumatic heart disease. On the other hand, they have never seen cardiac signs appear after the first 48 hours of treatment. One may hope that by early institution of hormone treatment, before the onset of carditis or in its early stages, cardiac sequelae may be prevented.

It is considered important to guard against the risk that the excess of adrenal hormones may cause water insufficiency, by restriction of fluid and salt intake, and

administration of mercurial diuretics if necessary. Interruption of treatment for 12 to 24 hours usually secures a prompt diuresis.

ACTH is given in doses of 75 mg. (less for small infants) daily in four regularly spaced injections; whereas cortisone is given by injection every other day. The dosage is not stated. Ideally, treatment should be continued for 2 weeks after disappearance of all clinical signs and terminated by progressive reduction of dosage. In acute articular rheumatism without carditis, or with incipient carditis, it may be given for 4 weeks; in severe cardiac rheumatism it should be continued for more than 2 months. *Kenneth Stone.*

Chronic Articular Rheumatism (Rheumatoid Arthritis)

Cortisone Therapy in a Case of Rheumatoid Nodules of the Eye in Chronic Rheumatoid Arthritis. MUNDY, W. L., HOWARD, R. M., STILLMAN, P. H., and BEVANS, M. (1951). *Arch. Ophthal., Chicago*, **45**, 531. 3 figs, 19 refs.

The case is described of a woman aged 50 with rheumatoid arthritis in whom bilateral episcleritis with nodular and plaque-like formations of the anterior sclera developed in both eyes. These gradually disappeared with topical cortisone therapy, but a severe recurrence appeared shortly after its cessation, with signs of anterior uveitis and secondary glaucoma. Considerable improvement took place after treatment with cortisone administered systematically. *H. E. Hobbs.*

Clinical Effects of Cortisone administered orally to Patients with Rheumatoid Arthritis. WARD, L. E., SLOCUMB, C. H., POLLEY, H. F., LOWMAN, E. W., and HENCH, P. S. (1951). *Proc. Mayo Clin.*, **26**, 361. 10 refs.

The oral administration of cortisone to patients suffering from rheumatoid arthritis produced an effective clinical response in 99 out of 100 cases. In 27 of these the hormone was given by the intramuscular route in the first instance, while in the rest it was administered orally throughout. The one case which failed to respond to oral administration responded satisfactorily to subsequent intramuscular injection.

In about one-half of the cases in which both routes were used effective oral and intramuscular doses were the same, while in the remainder an extra amount, which varied from one-sixth to one-quarter of the intramuscular dose, was required for oral administration. The speed of action was greater and its duration shorter by the oral route and in consequence divided doses were employed. In the 72 patients given cortisone by mouth only initial treatment for a period varying from 2 days to 2 weeks was required to establish the desired suppression of symptoms, the daily dose required ranging from 37·5 g. to 100 g. Subsequently it was found that in 21 per cent. of cases improvement could be maintained on a daily dose of 37·5 mg. or even less. The authors prefer to give lower initial suppressive doses than those originally advocated. They stress the need for the very gradual reduction of dosage if a low maintenance level is to be attained without relapse occurring. They state that the patient's needs appear to vary from time to time so that maintenance dosage can never be regarded as permanently established, even after many months of satisfactory suppression.

The side-effects observed in this series were no different from those observed in series treated with cortisone by the intramuscular route. In only two cases did gastro-intestinal irritation follow the oral administration of cortisone tablets. *W. S. C. Copeman.*

Synergistic Action of *para*-Aminobenzoic Acid and Cortisone in the Treatment of Rheumatoid Arthritis. WIESEL, L. L., BARRITT, A. S., and STUMPE, W. M. (1951). *Amer. J. med. Sci.*, **222**, 243. 14 refs.

The results presented in this paper demonstrate that sodium *p*-aminobenzoate enhances the action of cortisone in the treatment of rheumatoid arthritis. This substance was tried because it is known to inhibit inactivation of oestrogens by the liver; and there is a similarity in chemical structure between cortisone and the oestrogens.

In one group nine patients with rheumatoid arthritis were started on the usual dosage of cortisone acetate until maximum relief was obtained. The daily dose was then reduced to 25 mg. All patients relapsed. Sodium *p*-aminobenzoate was then given orally, 1·5 g. 2-hourly to a total of 12 g. daily, in addition to the 25 mg. of cortisone parenterally. Relief was again obtained; to approximately the same degree in five cases, somewhat less in three, and slightly greater in one.

In a second group six patients with rheumatoid arthritis were treated from the beginning with 25 mg. of cortisone acetate parenterally and 12 g. sodium *p*-aminobenzoate daily in divided doses of 1·5 g. 2-hourly. All patients showed improvement comparable to that obtained with cortisone in the usual doses.

Three detailed case reports are given. No undesirable side-effects were observed. Thus by the combined use of cortisone and sodium *p*-aminobenzoate rheumatoid arthritis can be controlled when the same dose of cortisone alone would be ineffective. *Kenneth Stone.*

Treatment of Rheumatoid Arthritis by Denervation of the Carotid Sinus. (Traitement de la polyarthrite chronique évolutive par énervation sinu-carotidienne.) LEGER, L., BIDAUT, H. (1951). *Pr. méd.*, **59**, 1351.

In the 2 years that have followed Lièvre's original suggestion (*Bull. Soc. med. Hôp. Paris*, 1949, **65**, 1256) of carotid-sinus denervation in the treatment of rheumatoid arthritis (in order to stimulate the adrenal cortex) the authors have operated on 32 cases, bilaterally in fourteen and unilaterally in eighteen. In eight there was no improvement, six derived transient benefit, another eight maintained improvement for periods of 6 to 8 months, four showed spectacular improvement, and others, recently operated upon, derived some benefit. There were two deaths.

Local analgesia was used by the authors, who discuss the indications for, and the dangers of, this operation. They conclude that it should be reserved for patients under the age of 50, and should be carried out before irreversible changes have taken place. They find it difficult to lay down any hard-and-fast rule on the advisability of unilateral or bilateral denervation. *D. Preiskel.*

Serial Vasography of the Peri-articular Vessels in Rheumatoid Arthritis. (Die Röntgen-Serienvasographie des periarticulären Gefäss apparates bei der rheumatischen Polyarthrose.) LEB, A. (1951). *Fortschr. Röntgenstr.*, **75**, 251. 5 figs.

Serial vasography in cases of primary progressive chronic articular rheumatism of the hand and wrist revealed important vascular changes, the most important of which was an arterial ischaemia. The arteries round

the joints were either narrowed or blocked. To this schaemia the author attributes the wasting of the periarticular tissues, and the atrophy of the articular cartilage without any noticeable reaction. The calcium content of the bone was normal to begin with, but later on the atrophy of the cartilage was followed by a secondary reorientation of the subchondral bone and by deformity of the edges of the bone.

The observed venous congestion was probably the result of the arterial changes. Comparison of the extensive vascular changes with the slight skeletal changes in the early stages of the disease suggests that the disease is primarily of vascular origin. *A. Orley.*

ACTH, Cortisone, and Other Steroids

Effect of Cortisone on Wound Healing. BANGHAM, A. D. (1951). *Brit. J. exp. Path.*, **32**, 77. 4 figs, 24 refs.

In experiments carried out at University College Hospital Medical School, London, the author found that cortisone given intramuscularly in daily doses of approximately 12·5 mg./kg. body weight had no effect on wound healing in guinea-pigs. In rats it had no dramatic effect either on the healing time or on the quality of the granulation tissue, which in some cases, however, was reduced in quantity. The administration of cortisone to rabbits in doses of 7·5 mg./kg. daily retarded wound healing. The effect of cortisone on wheal formation in rabbits following the injection of leucotactic peptides and of histamine was also studied. Before the injection of these substances the animal was given an intravenous injection of trypan blue: cortisone prevented the leakage of the dye into the tissues.

The author suggests that there may be some connection between the subduing effect of cortisone on the formation of granulation tissue and its apparent ability to protect small blood vessels from substances capable of increasing their permeability. If, as seems likely in the case of wound healing in rabbits, cortisone is merely depressing a normal process, its action is most probably to control the degree of reactivity rather than to alter its pattern. Whether cortisone exerts its effect throughout the process of wound healing is not known, but it is evident from the results obtained that cortisone is active in its earliest stages, namely, the stages of hyperaemia and oedema formation. *A. G. Riddell.*

Effect of Adrenocorticotropic Hormone (ACTH) on Beryllium Granulomatosis and Silicosis. KENNEDY, B. J., PARE, J. A. P., PUMP, K. K., BEYK, J. C., JOHNSON, L. G., EPSTEIN, N. B., VENNING, E. H., and BROWNE, J. S. L. (1951). *Amer. J. Med.*, **10**, 134. 20 figs, bibl.

ACTH and cortisone are known to alter cellular and fibrous-tissue reactions and to restore the serum albumin-globulin ratio. As beryllium granulomatosis shows cellular and fibrous-tissue reactions with hyperglobulinaemia a trial was made of ACTH treatment in two cases of this condition. Metabolic studies were carried out, together with respiratory function tests and radiological assessment, and detailed figures for the analyses of blood and urine are given.

ACTH, 100 mg. daily, was administered in the first case for 28 days, and in the second for three periods of 5 to 15 days. In both cases there was relief of symptoms and objective (*x*-ray) improvement during treatment. The development of oedema and emotional instability was noted during treatment. Cessation of hormone therapy was quickly followed by weakness, headache, and pyrexia for a week or two, and there was a return of the physical signs and of the *x*-ray opacities. The first patient maintained "some improvement" 2 months after therapy was completed, while the second had reverted to his previous condition within a month.

A case of simple silicosis was also treated, the dose of ACTH being increased to 160 mg. daily. In this case, cortisone also was subsequently administered. Symptomatic improvement occurred, with increased exertion tolerance. No changes in the *x*-ray appearance of the chest were seen, but the patient "remained improved".

Further study is indicated to discover whether ACTH is capable of promoting mobilization and excretion of beryllium from the tissues. It would seem that repeated short courses of ACTH may produce fewer complications. *L. W. Hale.*

Influence of STH, ACTH, and Cortisone upon Resistance to Infection. SELYE, H. (1951). *Canad. med. Ass. J.*, **64**, 489. 8 figs, 8 refs.

Evidence has accumulated that ACTH and cortisone can diminish resistance to infection both in experimental animals and man. The mechanisms responsible are not yet clearly understood, but it is possible that the general catabolic effect of the hormones, their inhibitory action upon granuloma formation, and their destructive action upon lymphatic tissues may be involved. The author, having noted that somatotrophic hormone (STH) acts antagonistically to ACTH in these respects, argued that it might be able to increase resistance to infection.

In one experiment, eight rats were given 10 mg. cortisone acetate by subcutaneous injection daily for 12 days; five died before completing the course; these and one survivor had multiple abscesses; all had lost a great deal of weight. A further nine rats, while receiving the same dose of cortisone, were also given 2 mg. STH daily; all survived and their average weight was unchanged. The experiment was repeated over a 17-day period with comparable results. In a second experiment cortisone was replaced by ACTH given subcutaneously in 2-mg. doses six times daily; five out of seven animals given ACTH alone had multiple abscesses, while all of seven given STH in addition remained healthy.

Microscopically, the animals in which there was abscess formation showed many large bacterial colonies throughout the lungs, kidneys, liver, and spleen (and in two cases on the peritoneum and in one on the endocardium) with almost no connective-tissue reaction. Identification of the bacteria has not been completed, and it remains to be established whether STH arrests the growth of the true pathogens or only of those normally non-pathogenic organisms whose proliferation is stimulated by an excess of glucocorticoids.

There is a brief discussion of the significance and possible explanations of these findings. *H. McC. Giles.*

Effects of 17-Hydroxy-11-dehydrocorticosterone upon the Adrenals of Normal and Hypophysectomized Rats maintained with Adrenocorticotropin. LEWIS, R. A., ROSEMBERG, E., and WILKINS, L. (1950). *Endocrinology*, **47**, 414. 7 refs.

Cortisone acetate (1·25 mg. daily) was injected into normal rats and into hypophysectomized rats maintained on a constant dosage (0·4 mg. thrice daily) of adrenocorticotrophin. The treatment reduced the weight and increased the cholesterol content of the adrenals in the normal rats, but had no such effects in the hypophysectomized animals. This is strong evidence that cortisone

produces these effects by reducing adrenocorticotrophin secretion. This would explain the beneficial results that have been reported (Wilkins, Lewis, Klein, and Rosemberg (1950), *Bull. Johns Hopkins Hosp.*, **86**, 249), when cases of adrenal hyperplasia are treated with cortisone.

Peter C. Williams.

Effects of ACTH and Cortisone on Antibodies in Human Beings. MIRICK, G. S. (1951). *Bull. Johns Hopk. Hosp.*, **88**, 332. 45 refs.

The author has studied the level of pre-existing antibody and antibody synthesis in patients treated with ACTH and cortisone. He vaccinated 59 patients with a single injection of a mixture of pneumococcal polysaccharides. Of these patients seventeen were treated with ACTH, and twelve with cortisone, and thirty were untreated. The production of mouse protective antibody to pneumococcus Type II was measured. Patients whose pre-vaccination serum neutralized more than 10 MLD of the pneumococci were eliminated from the series. Expressing the neutralizing capacity of the serum as the logarithm of the number of MLD's survived, the geometric mean of the titre of neutralizing antibody before vaccination was slightly greater in the control group (0·58 log) than in the treated group (0·41 log). After 10 to 21 days the figures were 3·75 log and 5·41 log respectively.

The effect of the titres of agglutinins for typhoid H antigen was studied in five patients with a titre of 1 in 10 or greater. In two the titres became fourfold to eightfold lower during treatment; in three there were no obvious changes. The titres of isohaemagglutinins for erythrocytes of different ABO blood groups were studied in eleven treated patients. In five patients (three receiving ACTH, two cortisone) the titre was fourfold higher during treatment than before. Serum globulin, measured by zinc sulphate turbidity, decreased in thirteen out of seventeen patients on ACTH and in six out of twelve on cortisone. The present evidence suggests that the beneficial effects of ACTH and cortisone in the treatment of hypersensitivity states and related diseases are not to be explained by suppressed antibody production.

The author discusses the apparently conflicting results which have been reported concerning adrenal effects on plasma proteins and antibodies in experimental animals and considers them to be due to species differences, the rat seeming to resemble man rather more closely than does the rabbit.

Harold Caplan.

Local Effects of Cortisone on Granulation Tissue and the Role of Denervation and Ischemia. SHAPIRO, R., TAYLOR, B., and TAUBENHAUS, M. (1951). *Proc. Soc. exp. Biol., N.Y.*, **76**, 854. 14 refs.

The authors found that the formation of granulation tissue around turpentine abscesses in the rat is modified if cortisone is mixed with the turpentine (0·5 mg. in 0·5 ml.). In comparison with control abscesses around 0·5 ml. turpentine alone, the granulation-tissue layer was thinner, the fibroblasts were smaller and less regular in formation, and the cellular infiltration was more profuse; vascularization appeared to be unaffected. Further experiments with cortisone-containing abscesses in ischaemic and in denervated tissues showed that these conditions did not materially modify the effects of cortisone on connective tissue outlined above. Although the mechanism of the inhibitory effect of cortisone on connective tissue is unknown, these experiments suggest that it is a direct local action rather than an action on either vasomotor mechanisms or the metabolism of nervous tissues.

B. E. W. Mace.

Sulfhydryl Inhibition as a Mechanism in the Effects of ACTH and Cortisone. ANDERSON, G. E., WIESEL, L. L., HILLMAN, R. W., and STUMPE, W. M. (1951). *Proc. Soc. exp. Biol., N.Y.*, **76**, 825. 1 fig., 14 refs.

The 11-oxysteroids are known to have an inhibitory effect on many cellular enzyme systems, and there is evidence to suggest that this action is due to reduction in availability of sulphydryl groups (-SH). Other substances also have this action, notably ascorbic acid through its oxidation product dehydroascorbic acid.

A series of estimations of the sulphydryl level in blood, in normal subjects and in patients with rheumatoid arthritis, showed that massive intravenous doses of ascorbic acid had no significant effect. The level was also found to be unchanged in rheumatoid arthritis, both before and after cortisone treatment. Another series of experiments was carried out with a hyaluronidase-indian ink mixture containing 75 turbidity units of hyaluronidase in 0·1 ml.; this amount was injected intracutaneously into the depilated skin of white mice. The hyaluronidase mixture spread further in the tissues than the saline control, but this effect was inhibited after the mouse had been given 2 mg. cortisone subcutaneously. Reduced glutathione (G-SH), 40 mg., was then given intraperitoneally; the original or increased skin spread was observed after a further injection of the hyaluronidase-indian ink mixture. A control experiment in which oxidized glutathione (G-SS-G) was used showed that this had no effect on the cortisone-inhibited skin spread.

B. E. W. Mace.

Clinical Significance of the Determination of Neutral 17-Ketosteroids in the Urine. (О клиническом значении определения нейтральных 17-кетостероидов в моче.) SCHULTZER, G. P. (1951). *Klin. Med., Mosk.*, **29**, 36. 1 ref.

Determinations have been made of the output and concentration of urinary 17-ketosteroids in healthy subjects and in patients suffering from adrenal disease. In a group of ten healthy women between the ages of 27 and 52 years the output ranged from 5·2 to 15·3 mg. in 24 hours, and the concentration from 0·4 to 1·2 mg. per 100 ml. In a healthy woman aged 33 who was observed over a period of 2 years the output varied from 9·8 to 22·5 mg. in 24 hours; and in a group of men with various suppurative conditions the average output was 12·4 mg. and the average concentration 1·3 mg. per 100 ml. Investigation was also made of thirteen patients with Addison's disease; the output of 17-ketosteroids varied from a trace to 2·8 mg. in three patients in whom the disease was due to tuberculosis, and from 2·3 to 11 mg. in four cases of different aetiology. Treatment with deoxycortone did not increase the output of 17-ketosteroids in three patients with tuberculosis of the adrenals, but raised the output to normal levels in three female patients with more benign forms of Addison's disease, and to 28·8 and 33·3 mg. respectively in two male patients. Hyperactivity of the adrenals led to increased output of 17-ketosteroids, and values up to 25·9 mg. in 24 hours were noted in two otherwise healthy persons suffering from acne; an output of 33·2 mg. was observed in a hermaphrodite and one of 30·2 mg. in a woman with Cushing's syndrome. The exceptionally high value of 806 mg. in 24 hours, with a concentration of 10·3 mg. per 100 ml., was found in a woman with a malignant adrenal tumour with widespread metastases.

D. J. Bauer.

Effects of "Artisone" Acetate and Cortisone in Patients with Rheumatoid Arthritis. LEFKOVITS, A. M., and SCHUPBACH, H. J. (1951). *Arch. intern. Med.*, **88**, 201. 8 refs.

A trial of "artisone" acetate in patients with rheumatoid arthritis revealed no beneficial effect. The patients were observed carefully; both clinically and biochemically, before, during, and after the administration of the drug, which was given in doses of 100 to 200 mg. daily. *D. P. Nicholson.*

Tuberculosis following Cortisone Therapy. Report of a Case of rapidly Progressive Pulmonary Tuberculosis following Cortisone Therapy for Rheumatoid Arthritis. KING, E. Q., JOHNSON, J. B., BATTEN, G. S., and HENRY, W. L. (1951). *J. Amer. med. Ass.*, **147**, 238. 3 figs, 7 refs.

This is a report of the case of a female, 39 years of age, who had been under medical care for 17 years, and who in 1947 developed rheumatoid arthritis, for which she was given cortisone in May, 1950. A radiograph of the chest was at that time clear. Cortisone had a good effect, and this was maintained for 4 months; when a relapse occurred in November, further cortisone was given, but was soon discontinued as the patient developed symptoms and clinical and radiological signs of a lesion at the right lung base. She died 2 months later, the radiological appearances being typical of an acute caseous tuberculosis.

Although no necropsy was performed, and although tubercle bacilli were never isolated, the authors consider that the patient died from a rapidly progressive tuberculosis, probably originating from old infective foci in the lungs which had broken down under the influence of cortisone on normal protective mechanisms.

B. E. W. Mace.

Effect of Adrenocorticotropic Hormone on Inflammation due to Tuberculin Hypersensitivity and Turpentine and on Circulating Antibody Levels. OSGOOD, C. K., and FAVOUR, C. B. (1951). *J. exp. Med.*, **94**, 415. Bibl.

Groups of guinea-pigs were sensitized by the subcutaneous injection of 2·5 to 5·0 mg. heat-killed tubercle bacilli and skin tested with tuberculin. The average diameter of the erythematous area was measured after 24 hours. Subsequently a daily dose of 20 to 30 mg. ACTH per kg. body weight was given at 8-hourly intervals for 16 days. At the end of this period and 2 weeks later the skin tests were repeated. It was found that under treatment with ACTH the erythematous area was significantly reduced in size; 2 weeks later it usually had reverted to its original size. Control groups treated only with saline did not show these changes. The complement-fixing antibody titre was not affected by ACTH; lymphocyte and eosinophil counts were decreased.

In another series, a group of six guinea-pigs received 0·1 ml. oil of turpentine intradermally. This caused an area of erythema and induration whose centre was necrotic. When ACTH was given in the same way as in the first series, the size of the central necrotic area remained unchanged, but that of the peripheral area decreased. It is suggested that the major role of ACTH is the suppression of tissue responses to injury. Its influence on antibody formation is regarded as uncertain.

H. Herxheimer.

Influence of Cortisone on Experimental Tuberculosis of Guinea-Pigs. KARLSON, A. G., and GAINER, J. H. (1951). *Dis. Chest*, **20**, 469. 4 figs, 16 refs.

At the Mayo Foundation 48 guinea-pigs each received a subcutaneous inoculation of 0·1 mg. virulent tubercle bacilli (H37Rv). On the 18th day 0·1 ml. 1 in 100 old tuberculin was injected intradermally into each animal, and on examination 48 hours later a positive reaction was seen in all of them. On the 20th day six animals which were killed to serve as controls were found to have gross lesions. On the 21st day the remaining 42 animals were divided into five groups: ten untreated controls, and four groups of eight each to be treated once daily with 6 mg. cortisone, 2 mg. streptomycin, 2 mg. cortisone, and 2 mg. streptomycin combined with 2 mg. cortisone, respectively. There was also a fifth group of six healthy animals to be treated with cortisone, and a sixth group to be treated with cortisone and streptomycin combined. Treatment in all cases continued for 62 days, when survivors were killed.

The results showed that administration of cortisone or cortisone with streptomycin was not beneficial, in that animals so treated failed to gain weight. Cortisone treatment also led to reduction in size of the tuberculin reaction and also in the number of reactions with necrosis. Post-mortem examinations showed that 6 mg. streptomycin once daily for 62 days caused a marked reversal of the progressive disease presumed to have been present when treatment was started. Administration of 2 mg. cortisone resulted in only partial inhibition of the disease. Of the group of eight animals given streptomycin with cortisone, six did not show even this partial improvement. The extent of the lesions in the animals given cortisone alone was comparable to that in the untreated controls.

Microscopically, the lesions in the animals treated with cortisone only were similar to those in the untreated animals. In those treated with 6-mg. doses of streptomycin the lesions seemed to be healing, whereas with 2 mg. there appeared to be a definite retardation of the disease. In the animals treated with both drugs the lesions were comparable in extent and appearance to those in the controls and in those given cortisone alone. The main effect of cortisone seemed to lie in preventing restriction of the disease by inhibiting fibrosis. Experiments *in vitro* showed that cortisone neither interfered with nor enhanced the bacteriostatic effect of streptomycin. *R. B. Lucas.*

Effects of Administration of the Adrenocorticotropic Hormone (ACTH) on Patients with Myasthenia Gravis. TORDA, C., and WOLFF, H. G. (1951). *Arch. Neurol. Psychiat., Chicago*, **66**, 163. 2 figs, 12 refs.

The effects of treatment with ACTH were studied in fifteen patients between the ages of 13 and 61 suffering from myasthenia gravis of 1 to 17 years' duration. Each patient received 25 mg. ACTH 6-hourly for 5 days, in addition to neostigmine and other therapy. Electromyographic studies and acetylcholine-synthesis determinations were carried out daily. During the last 2 days of administration of ACTH and for a few days thereafter a gradually increasing disability occurred, consisting mainly of asthenia, malaise, headache, and insomnia, and one patient with bulbar signs died on the third day of treatment. In the remaining fourteen cases improvement began during the first week after the last injection and continued for a few weeks. Improvement included increased well-being and increased work

performance on a reduced intake of neostigmine, and four patients were able to omit neostigmine altogether. Second and third courses of ACTH were given at intervals of 4 weeks to 10 months. Of the fifteen patients who were given 500 mg. ACTH, ten showed a second partial remission of considerable duration.

[These observations require confirmation; the risks in myasthenics already showing bulbar symptoms may be considerable.] *Hugh Garland.*

Cortisone Therapy in Boeck's Sarcoid. LOVELOCK, F. J., and STONE, D. J. (1951). *J. Amer. med. Ass.*, **147**, 930. 2 figs, 6 refs.

In the Bronx Veterans' Administration Hospital, New York, two patients in whom the diagnosis of sarcoidosis was proved by biopsy had extensive radiological changes in the lungs. After a preliminary period of observation they were treated with cortisone for 18 and 28 days respectively. In each case there was a marked improvement in the radiological appearances during treatment. The follow-up period was too short to evaluate the long-term effects. *P. C. Reynell.*

Cortisone Therapy in Sarcoidosis. Effect in a Case with Virtual Blindness. SILTZBACH, L. E., POSNER, A., and MEDINE, M. M. (1951). *J. Amer. med. Ass.*, **147**, 927. 3 figs, 2 refs.

The condition of a patient in the Montefiore Hospital, New York, suffering from sarcoidosis of the skin, enlarged mediastinal lymph nodes, and uveitis deteriorated during a 7-month period of observation until she was almost blind. She was then given cortisone intramuscularly for 15 weeks. The mediastinal lymph nodes became smaller and vision promptly improved, until it was 76 per cent. of normal when treatment was completed. When the injections were discontinued there was a slight relapse of the uveitis, but this was controlled by cortisone eye drops. After a further 6 months there was no other evidence of relapse. *P. C. Reynell.*

Favourable Response of Sarcoidosis to Cortisone Treatment. SMALL, M. J. (1951). *J. Amer. med. Ass.*, **147**, 932. 6 figs, 11 refs.

In the Halloran Veterans' Administration Hospital, Staten Island, N.Y., four patients with sarcoidosis were treated with cortisone for 4 to 6 weeks. Three of them had been observed for preliminary periods of several weeks, during which time the disease appeared to progress. In each case there was prompt symptomatic improvement and all objective manifestations of the disease regressed. The radiological improvement in the pulmonary lesions and the hilar lymph nodes was most striking, and in each case there was objective improvement in the results of pulmonary function tests. One patient showed marked improvement, although the radiological appearances suggested considerable pulmonary fibrosis and emphysema.

Three patients were followed-up for several months after treatment. In one there was some recurrence of skin, lymph-node, and pulmonary lesions, and in another the improvement was maintained, but in the third patient tuberculosis of the spine developed. In view of this last case the authors consider that there may be a real risk that patients with sarcoid may develop frank tuberculosis if treated with cortisone. *P. C. Reynell.*

Effect of Corticotropin (ACTH) in Chronic Ulcerative Colitis. Observations in Forty Patients. KIRSNER, J. B., and PALMER, W. L. (1951). *J. Amer. med. Ass.*, **147**, 541. 6 figs, 40 refs.

A series of forty patients with chronic ulcerative colitis (severe in 22 cases) were treated at the Frank Billings Medical Clinic, University of Chicago, with ACTH after having been under a period of observation. The ACTH treatment was preceded and followed by a period in which saline, which was represented to the patient as being ACTH, was injected. The total dose of ACTH ranged from 1 to 3 g., the largest being 7·92 g. in 126 days.

Clinical response was good in 27 cases—feeling of well-being increased, appetite improved, stools decreased in bulk and frequency, and fever abated; only four patients showed no improvement. The appearance of the mucous membrane improved greatly in twenty cases and less obviously in fourteen others; oedema and friability diminishing, but granularity persisting. In no case was a completely normal mucosa seen, and the radiological appearances remained abnormal. Laboratory investigations reflected this improvement. The erythrocyte sedimentation rate fell, faecal lyzozyme content diminished in four patients, and erythrocyte cholinesterase content fell. In the dosage used, ACTH produced side-effects (such as hypopotassaemia) in four cases, and withdrawal symptoms of malaise, fever, and muscle cramps occurred in almost half the total. The results were considered good, long courses of over 6 weeks being most effective, but the eventual relapse of twenty out of 36 originally benefited suggests that the effects of ACTH on ulcerative colitis is only temporary, although the relapses seemed to be of reduced severity. *K. Gurling.*

Clinical Studies on the Activity of Orally Administered Cortisone. THORN, G. W., RENOLD, A. E., WILSON, D. L., FRAWLEY, T. F., JENKINS, D., GARCIA-REYES, J., and FORSHAM, P. H. (1951). *New Engl. J. Med.*, **245**, 549. 8 figs, 23 refs.

The authors have carried out comparative studies of the clinical and physiological effects of cortisone given orally and by intramuscular injection. In general they found that oral cortisone has a quicker, more profound and less prolonged action than the same dose given intramuscularly.

The physiological activity of cortisone was estimated by the fall in circulating eosinophils. When 50 mg. was given orally there was a marked reduction in the eosinophil count after 4 hours, the count returning to normal within 24 hours (intravenous cortisone has a similar effect). When 50 mg. was given intramuscularly little change in eosinophil level could be detected after 4 hours; there was a fall later, which was still demonstrable at 24 hours. From the results presented it would seem necessary to give cortisone by mouth every 6 hours to maintain a useful level of activity.

Trials with "Compound F" and its acetate given by mouth indicated that these were more active by this route than was cortisone, and that the duration of action, particularly of free Compound F, was shorter. A further series of experiments showed that oral cortisone caused immediate sodium and chloride retention and potassium excretion in Addison's disease, and that this effect disappeared soon after discontinuance of the drug. This was in contrast to the delayed effects of intramuscular administration of cortisone. It is pointed out that

patients receiving oral cortisone are not protected, after withdrawal of the drug, from a period of adrenal insufficiency as are patients with intramuscular deposits from a series of injections. The authors also quote a case in which small doses of cortisone have been given orally to suppress adrenal hyperfunction in a case of adrenal virilism, with successful results.

Clinical investigations showed that a combination of deoxycortone acetate (DCA) and cortisone was a more satisfactory treatment for Addison's disease than DCA alone, as appetite, weight, and muscle strength were improved, anaemia was corrected, and hypoglycaemic complications were prevented. The successful oral use of cortisone to relieve an acute exacerbation of gout and also in a patient with chronic rheumatoid arthritis and pulmonary sarcoidosis is described.

The authors consider that cortisone is as effective orally as by intramuscular injection, but point out that the fact that it is so effective enhances the potential dangers of its indiscriminate use.

B. E. W. Mace.

Effects of Administering Adrenocorticotrophic Hormone by Continuous Injection to Normal Rats. INGLE, D. J., PRESTRUD, M. C., and LI, C. H. (1951). *Amer. J. Physiol.*, **166**, 165. 3 figs, 9 refs.

In this investigation 27 male rats approximately 300 g. in weight were given a high-fat, low-carbohydrate diet, and seventeen of them received continuous injection of ACTH in doses of 10 to 40 mg. daily for up to 21 days or until the animal became moribund. A control group of ten rats was given continuous injection of saline only for the same period.

Of the seventeen animals treated with ACTH ten were moribund within 12 to 20 days. All of them showed glycosuria on 2 or more days. This was only temporary in most cases, and disappeared while treatment was continued. Marked acetonuria occurred on 2 or more days in fourteen of the animals. All seventeen rats developed a negative nitrogen balance, but the peak of nitrogen excretion was not sustained, and in some cases fell to control values, during continued injection of ACTH. The rats lost weight rapidly during the first few days, the weight loss being closely related to the values for urinary non-protein nitrogen; the weight of the animals then remained relatively stable.

At necropsy three rats had diffuse infections involving the lungs, pleura, heart, liver, kidneys, and gut, and twelve had ulcers in the pyloric portion of the stomach, varying from multiple tiny ulcers to a few large deep ulcers which almost penetrated the mucosa and from some of which there was considerable loss of blood. Of the treated animals three had white spots penetrating the surface of the heart muscle, and eleven showed renal lesions consisting of grey patches penetrating the cortex, with occasional tiny nodules of hypertrophic tubules. None of the changes described was seen in the control animals.

Previous studies with cortisone had shown that doses of 10 mg. daily were necessary to produce effects comparable with those of continuous injection of ACTH, suggesting that the adrenal cortex of the rat can be made to secrete the equivalent of this amount of cortisone per day. The authors point out that the biological effectiveness of ACTH is much greater when it is given by continuous injection than when it is given intermittently.

Robert de Mowbray.

Effects of Administering Large Doses of Cortisone Acetate to Normal Rats. INGLE, D. J., PRESTRUD, M. C., and NEZAMIS, J. E. (1951). *Amer. J. Physiol.*, **166**, 171. 3 figs, 5 refs.

Male rats weighing approximately 300 g. were fed on medium-carbohydrate or high-fat diets. To 36 of them were given twice-daily subcutaneous injections of cortisone acetate in aqueous suspension in a total dosage of 5 to 20 mg. a day for up to 21 days or until the animal became moribund. A control group of 22 rats received injections of saline only.

Of the cortisone-treated rats twenty died, the mortality being greater with the higher doses. With a dose of 5 mg. cortisone daily none of the rats on the high-fat diet showed glycosuria or marked acetonuria, but ten of the twelve rats on a medium-carbohydrate diet and receiving the same dose of cortisone excreted glucose without acetone. With a dose of 10 mg. daily or higher all the rats developed glycosuria and generally acetonuria. The glycosuria was, however, only temporary. All the cortisone-treated rats developed a negative nitrogen balance, but the peak of nitrogen loss was not sustained, and in some animals a slightly positive balance was eventually re-established. Changes in weight were closely related to changes in nitrogen excretion. All the rats which received 15 to 20 mg. cortisone acetate daily died during the phase of rapid nitrogen excretion.

Of the treated rats nine had diffuse infections, with abscess formation, involving the lungs, pleura, heart, liver, kidneys, and gut; 21 had ulcers in the pyloric portion of the stomach; six had cardiac lesions; and 21 had renal lesions—all of them similar to those following administration of ACTH. In five of the rats on a high-fat diet visible lipaemia occurred after cortisone had been given for 14 days or more; the liver of these animals was fatty and whitish opacities appeared in the eyes.

The incidence of the lesions described was related to the size of the dose of cortisone. No lesions developed in control animals. *Robert de Mowbray.*

Human Adrenal Cortex after Administration of ACTH and Cortisone. Morphological Changes. O'DONNELL, W. M., FAFANS, S. S., and WEINBAUM, J. G. (1951). *Arch. intern. Med.*, **88**, 28.

The authors studied the histology of the adrenal glands at necropsy in fourteen cases treated with ACTH or cortisone at the University Hospital and St. Joseph's Mercy Hospital, Ann Arbor, Michigan. Frozen sections were stained with sudan III, and paraffin sections with haematoxylin and eosin.

The earliest response to ACTH was a reduction of sudanophilic substance and hypertrophy of the cells of the outer portion of the zona fasciculata. After more prolonged stimulation there was a progressive reduction in lipid content in all layers of the cortex and hypertrophy of cells in the fascicular and reticular zones. Since sudan-stained lipids give some indication of storage and secretion of adrenal cortical hormones or their precursors, the association of lipid depletion and hypertrophy of cortical cells was evidence of increased secretory activity. In contrast with the hypertrophy of the fascicular and reticular zones there was a reduction in width of the zona glomerulosa, though some of the cells in this zone were hypertrophic, suggesting that the transformation of glomerulosa cells into fascicular cells had been accelerated. There was thus evidence that the zona glomerulosa is stimulated by ACTH in man, in contrast with the findings in certain other species. In two of the nine cases treated

with ACTH the changes were interpreted as due to stress, since the dose of ACTH was inadequate, or the time-interval after treatment too long, to account for them.

After prolonged administration of cortisone there was atrophy of the zona fasciculata and zona reticularis, while the zona glomerulosa appeared to have increased in width and its cells were of normal size. Sudanophilic material was present, though in reduced concentration. The accumulation of lipid in conjunction with cellular atrophy in the inner cortex was regarded as evidence of storage of adrenal steroids or their precursors. The resemblance of these changes to those seen in cases of hypopituitarism suggests that cortisone induces adrenal cortical atrophy by suppressing the secretion of ACTH.

In two patients who died 17 and 51 days respectively after the last dose of cortisone there was evidence of a return to normal of cell size and lipid pattern, indicating that the cortical atrophy is reversible. *Robert de Mowbray.*

Levels of 17-Hydroxycorticosteroids in Peripheral Blood of Human Subjects. NELSON, D. H., SAMUELS, L. T., WILLARDSON, D. G., and TYLER, F. H. (1951). *J. clin. Endocrinol.*, **11**, 1021. 6 figs, 11 refs.

The 17-hydroxycorticosteroids in the blood of normal subjects and patients with various diseases were assayed by extraction with chloroform-ether, partition between 70 per cent. ethanol and hexane, chromatography on magnesium sulphate, and analysis by colorimetry on reaction with phenylhydrazine in sulphuric acid. The concentration in normal subjects was 4 to 10 μg. per 100 ml. of blood, and normal values were found in patients with rheumatoid arthritis and a variety of other diseases of varying severity; the only abnormal values found were in three cases of Addison's disease, in which where no 17-hydroxycorticosteroids were detectable in the blood, and in five dying patients whose blood contained 15 to 50 μg. per 100 ml. Paper chromatography of the material showed that it consisted mostly of Compound F; Compound E was not present but Compound S might be. Arteriovenous differences in concentration of 17-hydroxycorticosteroids, if present, were less than the error of the method (±20 per cent.) even in areas of acute inflammation. The blood level was increased by the injection of ACTH, but the effect was short-lived unless the hormone was given by intravenous drip. The increased levels found in the dying patients were about equal to those produced by the intravenous infusion of 15 mg. ACTH during 24 hours.

Peter C. Williams.

Eosinopenic Response to Cortisone and ACTH in Normal Subjects. KELLGREN, J. H., and JANUS, O. (1951). *Brit. med. J.*, **2**, 1183. 3 figs, 10 refs.

In this study of the eosinopenic response to cortisone and ACTH the number of circulating eosinophil leucocytes was estimated in a counting chamber by a modification of Dunger's method in four healthy male subjects, aged 32 to 43, under normal working conditions. Duplicate readings differed by +5 per cent. for counts of 100 per c.mm. or over, though with very low counts the error was greater.

Morning counts were made between 9.30 and 10 a.m. They varied by up to 300 per cent. on different days in any one subject, and differed considerably as between one subject and another. On control days the eosinophils were counted at 2-hourly intervals, and the mean fluctuation throughout the day was no more than 10 per cent. of the morning count in any one subject, though occasionally there was an increase or decrease of about 40 per cent. On other days ACTH or cortisone, in single doses of 2·5 to 100 mg. intramuscularly or 6·25 to 100 mg. orally respectively, was given immediately after the morning count. The fall in eosinophil count began within 2 hours and was pronounced at 4 hours. With the higher doses the count continued to fall at 6 hours and was still low at 8 hours, whereas with the lower doses the count increased again at 6 hours and tended to return to the morning level or above after 8 hours. The 4-hour and 6-hour counts therefore gave the most information. Repeated injections of the same dose did not give strictly comparable curves of eosinophil response, which was not considered surprising, in view of the spontaneous fluctuations of the eosinophil count already described.

The responsiveness to ACTH and cortisone differed considerably as between the four subjects, and the response to ACTH differed from the response to cortisone in two of the subjects. The two who gave satisfactory eosinopenic responses to small doses of both hormones also showed a wide range of fluctuation in their morning counts, whereas the other two who were less responsive, showed smaller variations in their morning counts.

An acute febrile stress was induced by 10 ml. T.A.B. intravenously in two patients with rheumatoid arthritis and also in the four subjects of this study. The fall in eosinophil count was in each case about equivalent to that which followed a single injection of 25 mg. ACTH, though it was of longer duration. In three cases of panhypopituitarism there was a greatly exaggerated and prolonged eosinopenic response to oral cortisone.

Robert de Mowbray.

Effect of Sodium Salicylates on Circulating Eosinophils and Urinary Uric-acid : Creatinine Ratio in Healthy Volunteers. ROSKAM, J., CAUWENBERGE, H. VAN, and MUTSERS, A. (1951). *Lancet*, **2**, 375. 2 figs, 4 refs.

Ten normal students were given large doses of sodium salicylate by mouth; four received 4 g. and six received 6 g.; two similar subjects acted as controls. Eosinophil counts were made immediately before the dose, then at hourly intervals for 6 hours, and finally 8 hours afterwards. Counts were made on samples of venous blood by the direct eosinophil method, using Dunger's fluid; at the same intervals of time the plasma salicylate was estimated by Van Cauwenberge's method. The urinary uric acid: creatinine ratio was calculated every 2 hours.

In agreement with the observations of Meade and Smith (*Lancet*, 1951, **1**, 773) the authors found no significant decrease in the number of circulating eosinophils during the first 4 hours following salicylate administration. However, a marked decrease was observed from the fourth to sixth hours. Different dosage and different time of observation would therefore account for discrepancies in the reports from the two laboratories. The delayed decrease in the amount of circulating eosinophils when salicylate is administered by mouth seems to be due to the slowness of intestinal absorption of the drug.

The urinary uric acid: creatinine ratio which increased significantly by the second hour, an event which, like eosinopenia, is indicative of oversecretion of cortical factors. *Nancy Gough.*

Some Observations on Endogenous Cortisone Excretion in Man. COPE, C. L., BOYSEN, X., and MCCRAE, S. (1951). *Brit. med. J.*, **2**, 762. 7 figs, 11 refs.

Endogenous cortisone excretion was estimated by comparing the fall in the eosinophil-cell count (in

adrenalectomized mice) produced by urinary extracts, with that produced by cortisone acetate. Cortisone and Compound F are the only known substances that will produce such a fall, and as both have been isolated from urinary extracts prepared in a similar way the test is presumably specific. The extract will probably contain an unknown proportion of Compound F but the activity is expressed as if it were all due to cortisone. The volume and nature of the solvent are important, as slight variations in these affect the absorption from the subcutaneous site and consequently the eosinophil-cell response; 0·5 ml. of 20 per cent. propylene glycol was used in the present tests. Each urine sample was tested by injection into three mice and this requires the urine excreted during 12 to 48 hours. The methods used have already been described (Cope, C. L., *Brit. med. J.*, 1951, **1**, 271; *Abstracts of World Medicine*, 1951, **10**, 72).

The daily excretion was 40 to 120 μg. in the absence of stress, and 170 to 320 μg. during "medical" stress or during late pregnancy. When patients were injected with 100 mg. ACTH daily there was a progressive rise to levels of 250 to 650 μg. per day. The injection or oral administration of cortisone increased the output within a day, but the extra activity in the urine only represented 0·2 per cent. of the exogenous material. The cortisone output was subnormal in seven cases of Addison's disease and in four of panhypopituitarism; it never amounted to more than 70 μg. per day, and in six cases was indetectable.

Ephedrine given orally (65 mg. thrice daily) to one patient doubled the cortisone output, but a lower dosage (32 mg. thrice daily) was incapable of maintaining an increased rate produced by ACTH treatment.

It is concluded that the test is reliable enough to "reveal the more gross variations of cortisone output in man" and is probably a better index of adrenal function than the patient's own eosinophil count or the chemical estimation of reducing steroids in the urine. Cases are discussed in which these tests did not agree with the rate of cortisone excretion. *Peter C. Williams.*

Treatment of Hemorrhagic Shock with Cortisone and Vitamin B^{12}. HOWARD, J. M., and DEBAKEY, M. E. (1951). *Surgery*, **30**, 161. 2 figs, 5 refs.

The authors observed the effect of cortisone and vitamin B^{12} on haemorrhagic shock in dogs, which were bled until the blood pressure fell to 30 mm. Hg, and then maintained at that level by subsequent small bleedings and small transfusions until a state of irreversible shock was reached; this point was indicated by the inability of the shocked animal to maintain his blood pressure at the level of 30 mm. Hg despite repeated transfusions. Under these conditions it was demonstrated that neither cortisone nor vitamin B^{12} had any significant effect upon the course of haemorrhagic shock. *K. Whittle Martin.*

Thromboembolic Complications associated with ACTH and Cortisone Therapy. COSGRIFF, S. W. (1951). *J. Amer. med. Ass.*, **147**, 924. 7 refs.

The author, working in the Presbyterian Hospital, New York, has found that 28 patients out of 700 receiving ACTH or cortisone therapy had one or more thrombo-embolic complications, with a total of forty episodes. Increased coagulability of the blood had previously been noted in patients treated with ACTH and cortisone, and the purpose of the analysis of the clinical data of these 28 patients was to determine if possible the relationship between the thrombo-embolic complications and the hormone therapy.

Of the 28 patients, 21 (75 per cent.) were aged between 40 and 79, the age range in which thrombotic disease is usually encountered. Of the forty thrombo-embolic episodes, nineteen occurred in patients confined to bed, eight in semi-ambulatory patients, and thirteen in ambulatory patients. Most of the patients were suffering from diseases in which cortisone or ACTH therapy is usually considered to be of some value, twelve being under treatment for rheumatoid arthritis. Some of the patients, however, had septic conditions which might predispose to thrombotic complications. Thrombo-embolic episodes occurred equally in the ACTH- and cortisone-treated cases; nineteen of the 28 patients had received cortisone or ACTH for 3 weeks, others for longer periods up to 9 months, before the onset of the thrombosis. In eight patients, the first thrombo-embolic episodes occurred during hormone therapy, and in ten after it has been discontinued; in seven of these ten they occurred within one week of stopping the treatment. Thrombo-embolic complications occurred more frequently in those receiving the higher doses of cortisone or ACTH.

The author points out that comparative statistics which would indicate the incidence of thrombotic phenomena in a similar group of patients are not available, but he considers nevertheless that the occurrence of forty thrombotic episodes in 28 patients from among 700 patients receiving cortisone or ACTH therapy is greater than would be expected. *C. E. Quin.*

Effects of Cortisone on the Mechanism of Increased Capillary Permeability to Trypan Blue in Inflammation. MENKIN, V. (1951). *Amer. J. Physiol.*, **166**, 509. 3 figs, 23 refs.

The local increase in capillary permeability normally resulting from the intradermal injection in rabbits of inflammatory exudates obtained by the intrapleural or intraperitoneal injection of various irritants into dogs and rabbits was shown to be inhibited when the exudate was mixed with adrenal cortical extract or with cortisone in the case of alkaline exudates, whereas no such inhibition occurred with acid exudates. That the effect of cortisone and adrenal cortical extract is not determined simply by adding lactic acid to the alkaline exudate and sodium hydroxide to the acid exudate before injection without altering the results obtained. It is therefore suggested that "concomitantly with the developing acidity in the later phase of the inflammatory reaction, there is liberated in abundance a factor, other than leukotaxine, capable of sustaining the increase in capillary permeability throughout the length of the acute inflammation". The name "exudin" is proposed for this factor, which appears to supplement leukotaxine. The relationship of exudin to physiological homeostasis is discussed.
Kathleen M. Lawther.

Effects of ACTH on the Mechanism of Increased Capillary Permeability to Trypan Blue in Inflammation. MENKIN, V. *Amer. J. Physiol.*, **166**, 518, 3 figs, 8 refs.

The increase in capillary permeability induced by acid inflammatory exudates containing exudin is inhibited by ACTH which, in contrast to cortisone, fails to suppress the like action of leukotaxine. Cortisone on the other hand is ineffective against exudin. It is therefore suggested that the combination of cortisone and ACTH would seem to be a more effective means of restricting acute inflammatory exudation of acid than either alone,

because of the presence of some leukotaxine and much exudin in acid exudates. The possibility of more effective therapy for rheumatoid conditions is discussed in the light of these findings. *Kathleen M. Lawther.*

Histological Study of the Effect of Cortisone on Wound Healing *per primam*. An Experimental Study. COLE, J. W., ORBISON, J. L., HOLDEN, W. D., HANCOCK, T. J., and LINDSAY, J. F. (1951). *Surg. Gynec. Obstet.*, **93**, 321. 8 figs, 6 refs.

An experimental study of wound healing in dogs showed that cortisone (Compound E) administered subcutaneously (2 mg./kg. body weight) had no demonstrable effect on the healing of clean wounds. This contrasts with the observations of other workers on granulating wounds, where ACTH may retard the healing process. *Guy Blackburn.*

Effect of ACTH and Cortisone on Wound Healing. An Experimental Study. ALRICH, E. M., CARTER, J. P., and LEHMAN, E. P. (1951). *Ann. Surg.*, **133**, 783. 5 figs, 13 refs.

The authors, working in the Department of Medicine of the University of Virginia, have investigated the influence of ACTH and cortisone on the strength and histological characters of healing experimental abdominal wounds in male albino rats of the Wistar strain maintained on a standard laboratory diet. An incision was made through all the layers of the abdominal wall in the midline and sutured in two layers. Animals were killed at 2-day intervals up to 12 days after operation, and strips of tissue 1 cm. wide were cut transversely across the wound and their tensile strength measured in grammes. The animals were divided into five groups, which were treated as follows:

(1) no treatment before or after operation;

(2) injection of 0·5 ml. saline twice daily from 2 days before operation;

(3) bilateral adrenalectomy performed 1 week before operation, 0·85 per cent. saline being given in drinking water;

(4) 0·5 or 1·0 mg. ACTH injected intramuscularly 6-hourly from 3 days before operation;

(5) 3·0 mg. cortisone injected intramuscularly twice daily from 2 days before operation.

Healing, as shown by tensile strength, was normal in Groups 1, 2, and 3, and also in animals receiving 2 mg. ACTH daily. When 4 mg. ACTH was given daily a moderate retardation of healing occurred. In Group 5 there was marked retardation of healing. Histological examination revealed delay in formation of granulation tissue in the animals of Groups 4 and 5, though the effects were less striking in the latter. It was also noted that proliferation of blood vessels was abnormal in Group 5, sharply delimited focal groups of capillaries being observed at the healing surface of the wound. A relatively large, round, clear cell with apparent vacuolization was also observed at the healing surface in Group 5. It resembled the " foam cell " (*Gitterzelle*) of the central nervous system, and was absent in sections from control animals and those treated with ACTH. *C. E. Quin.*

Problems Arising in Treatment with Cortisone and ACTH. (Problèmes posés par l'emploi thérapeutique de la cortisone et de l'ACTH.) COSTE, F., DELBARRE, F., LAURENT, F., and LACRONIQUE, F. (1950). *Presse méd.*, **76**, 1337.

This article consists, firstly, of a résumé of the known effects of cortisone and ACTH in rheumatic and non-rheumatic affections, and, secondly, of a discussion of the problems that arise from their use. Possible Modes of action are suggested for some of the conditions in which these hormones are known to be effective: it is pointed out that they never strike at the root of a disease, but only suppress, temporarily, the normal reactive processes of the organism (except in adrenal deficiency). The authors discuss the problems of relapse and of adrenal hypofunction, after cessation of treatment, and the dangers arising from hyperadrenalism and from the masking of signs of infection.

After a survey of the respective indications for ACTH and cortisone, the authors conclude that cortisone will be more widely used; while the treatment of acute illness is effective, often spectacularly so, that of chronic states is, as yet, difficult to assess. *B. E. W. Mace.*

Studies of Urinary 17-Ketosteroid Excretion by means of a New Micro-Chromatographic Fractionation Procedure. ZYGMUNTOWICZ, A. S., WOOD, M., CHRISTO, E., and TALBOT, N. B. (1951). *J. clin. Endocrinol.*, **11**, 578. 9 figs, 21 refs.

A procedure is described, a modification of that originated in Amsterdam by Dingemanse and her colleagues (*J. clin. Endocrinol.*, 1946, **6**, 535), which enables qualitative as well as quantitative studies to be made of the urinary 17-ketosteroids. The method only requires 0·3 mg. ketosteroid, which is the quantity contained in a 3-hr sample of normal urine.

The urine is hydrolysed and extracted either at the same time with toluene or later with carbon tetrachloride or ether. The extract is washed with alkali and the ketonic fraction separated with Girard's reagent P, dried and redissolved in benzene. The ketosteroid content of this solution (and in subsequent fractions) is determined colorimetrically by the Zimmerman reaction and an appropriate dilution made, containing about 0·3 mg. in 5 ml. benzene, for chromatographic fractionation. This solution is percolated through an alumina column and eluted in forty separate fractions by the addition of solutions of methanol in benzene, rising progressively from 0·05 per cent. to 0·5 per cent., and finally of absolute methanol. When the amounts of ketosteroid (expressed as a percentage of the total) contained in successive fractions are plotted graphically, the graph has a characteristic shape with six major peaks and one minor. The positions of these corresponds with the positions occupied by various pure steroids subjected to the same procedure. The addition of pure steroid to a urine extract heightens the peak at its characteristic position, but does not otherwise affect the shape of the graph. Almost identical curves are obtained from the same individual at different times or from the same sample of urine subjected to different conditions of preliminary hydrolysis and extraction. Warnings are given regarding the preservation of the alumina and about maintenance of constant dimensions in the column. Preliminary fractionation with Girard's reagent is essential, as non-ketonic materials cause alterations in the form of the graph. It is advisable to use the same amount (0·3 mg.) of ketosteroid for each fractionation; quantities less than 0·27 mg. yield separate fractions too small for colorimetric determination.

Individual values and mean curves are given for six normal men and four normal women; the two curves are generally similar, but men tend to excrete proportionately more ketosteroid at Peaks II and VI (Fractions 6-7 and 34-35) and women at Peak IV (Fractions 17-25). Very

high total ketosteroid excretion was found in five cases of congenital adrenal hyperplasia and was associated with abnormally high values at Peak III and low values at Peak IV, whereas in another case, which was probably not congenital, Peak III was normal, but an abnormal peak was present in Fractions 8-12. In two cases of burns, one of acute peritonitis, and one of " inflammatory breast cancer ", abnormal curves of the same general type were obtained, suggesting that there is a qualitative as well as quantitative change in adrenal metabolism in conditions of stress, and that this resembles that due to pathological hyperplasia. Other cases of malignant disease gave abnormal curves of different types, but normal curves were also recorded. Administration of ACTH to two boys produced curves which differed in the two cases and on different occasions, providing evidence of variation in adrenal responsiveness. Since these abnormal curves are present in men and women to the same extent, it is fair to assume that they indicate changes in adrenal, rather than gonadal, activity. *Peter C. Williams.*

Intravenous Use of ACTH. McINTOSH, H. W., and HOLMES, C. B. (1951). *Canad. med. Ass. J.*, **65**, 33. 1 fig., 2 refs.

The authors have studied the effect of ACTH given intravenously in two subjects by means of the fall in eosinophil count and the rise in 17-ketosteroid excretion. To one subject ACTH was administered by drip transfusion over 24 hours every 5 days, observations being made with doses of 0, 2·5, 5, 10, 20, 40, 80, and 160 mg. A dose of 5 mg. in 24 hours resulted in almost total disappearance of eosinophil, leucocytes, and the 17-ketosteroid excretion was significantly increased. A 10-mg. dose caused a rather greater 17-ketosteroid excretion, but with larger doses than this the excretion of significantly greater amounts did not occur. The eosinophil count and 17-ketosteroid level returned to normal the day after transfusion, except that when doses of 80 and 160 mg. were used the effect was partly sustained for a second day. ACTH given intramuscularly, 20 mg. every 6 hours, produced only a slight effect on eosinophil count and 17-ketosteroid excretion.

To the other subject a fixed amount (20 mg.) of ACTH was given by intravenous drip, but the length of time taken to give this was varied from 1 minute to 24 hours. It was shown that the full effect was obtained only when the ACTH was given for 12 or 24 hours.

These results suggest that there is a minimum dose of ACTH (5 to 10 mg.) which, given intravenously over 24 hours, will produce a maximum degree of adrenocortical stimulation; that larger doses are no more effective and therefore wasteful; and that much of the physiological activity of ACTH is destroyed when given intramuscularly. *B. E. W. Mace.*

Limitations of the ACTH-regulating Effect of Corticoids. FORTIER, C., YRARRAZAVAL, S., and SELYE, H. (1951). *Amer. J. Physiol.*, **165**, 466. 26 refs.

Neural Control of the Pituitary Gland. I. The Neurohypophysis. II. The Adenohypophysis, with Special Reference to the Secretion of ACTH. HARRIS, G. W. (1951). *Brit. med. J.*, **2**, 559 and 627. 8 figs, bibl.

Use of Oral Cortisone in Paediatrics. WOLMAN, B. (1951). *Brit. med. J.*, **2**, 1246. 10 refs.

Thrombo-Embolic Complications in Cortisone and ACTH Therapy. (Accidents thrombo-emboliques des traitements par la cortisone et l'hormone corticotrope hypophysaire.) COSTE, F., GALMICHE, P., PIGUET, B., DELBARRE, F., and LAURENT, F. (1951). *Rev. Rhum.*, **18**, 189.

Local Treatment with Cortisone. (À propos des traitements locaux par la cortisone.) COSTE, F., GALMICHE, P., and BOREL, M. (1951). *Rev. Rhum.*, **18**, 205.

Use of Cortisone and ACTH in Gold Dermatitis. (Emploi de la cortisone et de l'ACTH dans les aurides.) COSTE, F., PIGUET, B., DELBARRE, F., and OURY, M. (1951). *Rev. Rhum.*, **18**, 224.

Acute Psychosis during ACTH Treatment. Recovery with Cortisone. Discussion of Pathogenesis. (Psychose aigue au cours d'un traitement par l'ACTH. Guérison par la cortisone. Discussion pathogénique.) COSTE, F., PIGUET, B., BERTAGNA, L., and FLAVIGNY, H. (1951). *Rev. Rhum.*, **18**, 193.

Administration of Cortisone by the Aerosol Method in the Treatment of Bronchial Asthma. GELFAND, M. L. (1951). *New Engl. J. Med.*, **245**, 293. 14 refs.

Oral Cortisone Therapy in Allergic Diseases. FRIEDLAENDER, S., and FRIEDLAENDER, A. S. (1951). *J. Allergy*, **22**, 291. 1 fig., 10 refs.

Generalized Erythrodermia occurring in a Case of Psoriasis on Treatment with Adrenocorticotropic Hormone (ACTH). COHEN, D., and DISTELHEIM, I. H. (1951). *J. invest. Derm.*, **17**, 61. 2 figs, 6 refs.

Potentiating Effect of ACTH and of Cortisone on Pressor Response to Intravenous Infusion of L*Nor*-epinephrine. KURLAND, G. S., and FREEDBERG, A. S. (1951). *Proc. Soc. exp. Biol., N.Y.*, **78**, 28. 2 figs, 17 refs.

Effect of Cortisone on Reaction of Skin to Ultra-violet Light. JÄRVINEN, K. A. (1951). *Brit. med. J.*, **2**, 1377. 11 refs.

Other General Subjects

Periosteal Dysplasia (Porak and Durante's Disease). (Dysplasie périostéale ou maladie de Porak et Durante.) DEBRÉ, R., MOZZICONACCI, P., GRUMBACH, R., and ATTAL, C. (1951). *Sem. Hôp. Paris*, **27**, 1345. 19 figs, 44 refs.

The authors describe five new cases of periosteal dysplasia. The clinical features of each of the cases are briefly discussed and the morbid anatomy and histology of two are described in detail. A general clinical and radiological picture is then presented.

There was no relevant family history. At birth the infant had a small body but a large head, not hydrocephalic in type. The cranial vault had retained its cartilaginous consistency and was parchment-like to palpation. The face was normal except for a parrot-beak nose. Proximal limb segments were curved, thickened, and deformed. Extremities were normal in size and shape. The thorax was deformed and the sternum projected forward, while the ribs showed signs of old and recent fractures. The bones, though bulky, were pliant, the joints lax, and the muscles hypotonic. Radiologically, the cranial vault was not ossified. The shafts of the long bones were thickened, widened, and made bulky as a result of numerous intra-uterine fractures, but the epiphyses appeared normal. There was

no visceral or mental abnormality, but immobility was striking, with inability to raise the head or move the limbs. New fractures appeared without apparent reason. The skull became flattened posteriorly and enlarged transversely, and the fontanelles remained large. Histologically, the periosteum was fibrous and thickened, while in the subperiosteal layers ossification was poor and disorganized. At the site of fractures the cartilage was thicker and more active, as though conditions for ossification were more favourable. In three cases death occurred in the first year, one patient was still under observation at one year, and one was alive, a deformed dwarf, at six years.

The condition described, claimed by Porak and Durante to be a disease entity, is compared with achondroplasia (Lobstein's disease). The authors conclude that only genetic studies and embryological researches will decide whether the two conditions are quite distinct or simply variations of the same genetic fault. *J. M. Alexander.*

Neurogenic Factor in Rheumatic Inflammation. KELLY, M. (1951). *Med. J. Aust.*, **1**, 859. 11 figs, 31 refs.

It is suggested that at the site of any referred pain the release of a " pain substance " may set up all the signs of inflammation, with hyperaemia, exudation, joint effusion, and other changes, and thus provide a new primary site for further reflex spread. Various examples are given both of cases of synovitis cured by treatment of a remote primary focus and of production of synovitis by distant trauma. [Some are surprising: for example, an effusion in the left knee of a patient with rheumatoid arthritis 2 days after aspiration of the right knee is attributed to reflex causes. Traumatic primary foci are included in this theory, but the fact that they do not spread is not explained. The author does not claim that neurogenic factors are the sole means of spread of rheumatic inflammation, but his argument that they play a predominant part is not convincing.] *H. F. Turney.*

Experimental Determination of the Hypertensive Diathesis in Man. CREGER, W. P., CHOY, SUN HAK, and RANTZ, L. A. (1951). *J. Immunol.*, **66**, 445. 6 refs.

To determine whether abnormally large quantities of antibody are produced in response to antigenic stimulus the authors injected 1 ml. blood of a heterologous group into a series of experimental subjects and tested their response by assessing the titre at which the donor's erythrocytes were clumped by the recipient's serum at intervals of 1 or 2 weeks. The chosen subjects were a group of medical students and a small group of patients suffering from such conditions as rheumatoid arthritis, inactive rheumatic fever, and disseminated lupus erythematosus.

The authors found that two out of 25 medical students responded with abnormally high agglutinin titres. Among the patients, one suffering from lupus erythematosus, one with erythema nodosum, one with acquired haemolytic anaemia, and three with inactive rheumatic fever, reacted with an unusually high antibody response, but none of three patients suffering from rheumatoid arthritis showed an abnormal response.

The authors conclude from this preliminary work that a small number of both normal subjects and patients suffering from certain diseases have an immunological hyperactivity; they point out, however, that further confirmatory work is needed. *W. Tegner.*

Does the Adrenal Cortex play any Part in the Causation of the so-called Diseases of Adaptation ? (Le cortex surrénal joue-t-il un rôle dans la genèse des maladies dites de l'adaptation ?) COSTE, F., GALMICHE, P., and DELBARRE, F. (1951). *Presse méd.*, **24**, 481.

Selye's theory of the " General Adaptation Syndrome " holds that the responses to " stress " may be a pathological one, and that it may be the result of an absolute or relative excess of secretion of mineralo-corticoids. Experiments on rats showed that an inflammatory arthritis may be produced, under certain conditions, by the administration of large doses of desoxycorticosterone. This article is a discussion of this point, and of its application to inflammatory arthritis in man.

The following questions are raised:

(1) Is desoxycorticosterone a naturally occurring adrenal steroid ? It is present, in minimal quantity, in adrenal tissue, but has never been isolated from adrenal venous blood. It is possibly only present as a precursor of another steroid.

(2) If desoxycorticosterone is not a naturally occurring steroid, is it possible that it is formed in significant quantity in the tissues from a normal adrenal hormone ? This remains an hypothesis, as there is little experimental evidence. Present methods of estimation of the rate of excretion of steroids are unsatisfactory and unreliable.

(3) Tests of adrenal function in rheumatoid arthritis. The work of the authors has not shown any adrenal dysfunction.

(4) Can desoxycorticosterone be shown to play a part in the production of human arthritis, from the results of treatment with this substance ? Patients with Addison's disease, when treated with DOCA and salt, inconstantly develop rheumatic symptoms: in this case, the gluco-corticoids, the antagonists, are absent. With normal adrenal function, DOCA, even in high dosage, does not cause any form of rheumatism. Deprivation of chloride, effective in preventing the occurrence of arthritis in Selye's DOCA-treated animals, has no effect on human polyarthritis.

(5) Is it possible that the normal regulation of adrenal secretion can be modified to produce an hyperhormonal or dyshormonal state which would be the cause of the diseases of adaptation ? Sayer's theory, for which there is considerable evidence, suggests that this modification is immediate and exact: stress results in increased utilization of adrenal steroids, and the hypophysis immediately increases its output of ACTH to maintain the normal corticoid level. Hypercorticism and dyscorticism thus do not occur, and a theory demanding these states as a basis for the diseases of adaptation is difficult to maintain. Hypertrophy of the adrenal cortex is a usual finding in these diseases, but this is no evidence of abnormal adrenal function.

[This thoughtful paper thus throws considerable doubt on the validity of Selye's theories, and the authors suggest that more evidence is necessary before they can be accepted.] *B. E. W. Mace.*

Death with Anti-Histamine Medication. (Letal komplikation vid antihistamin-medikation.) TÖRNQVIST, S. (1951). *Nord. Med.*, **46**, 1311. 1 ref.

A two-year-old boy after having been given 0·15 g. of an antihistaminic, β-dimethylaminoethylbenzohydryl ether hydrochloride, died in status epilepticus. *G. M. Findlay.*

Ocular Manifestations of Rheumatism. (Àpropos des manifestations oculaires du rhumatisme.) MAIGNIEN-COURARD, A. (1951). *Gaz. méd. France*, **58**, 445. 18 refs.